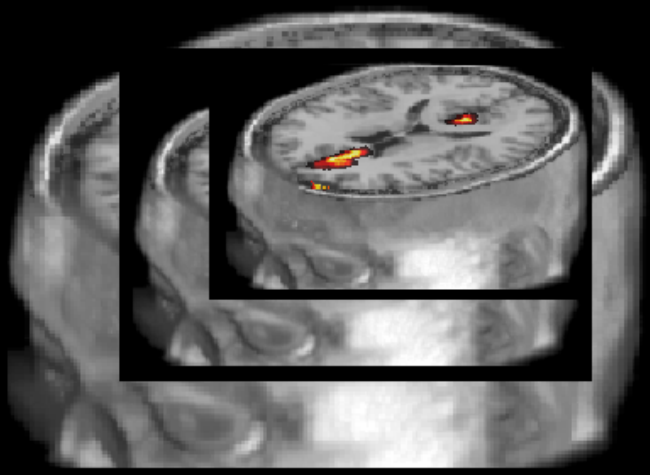


Antonio P. Strafella M.D. Ph.D. FRCPC

Dept. Medicine/Neurology, UHN.
Toronto Western Research Inst., UHN
PET Imaging Center, CAMH.

University of Toronto

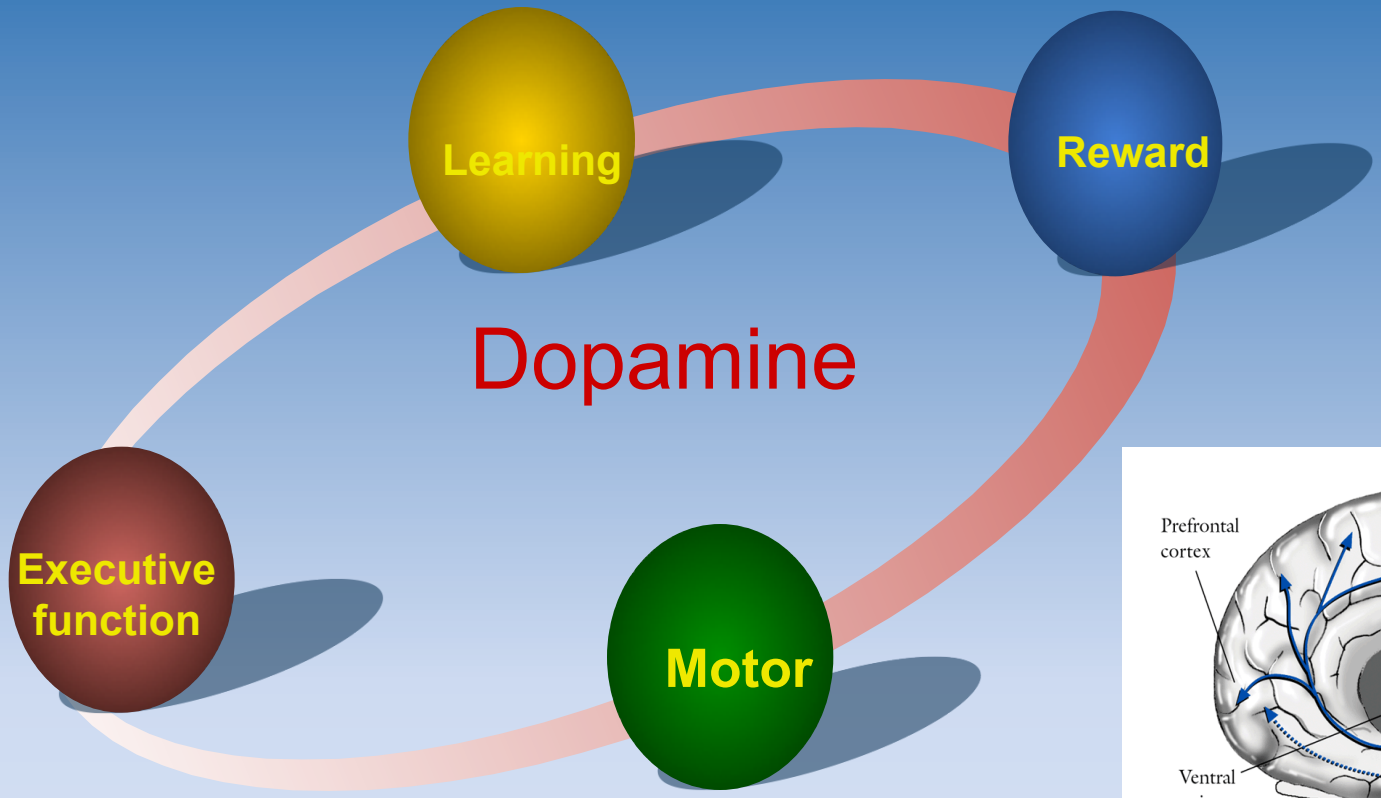
HBM 2014- Educational Course:

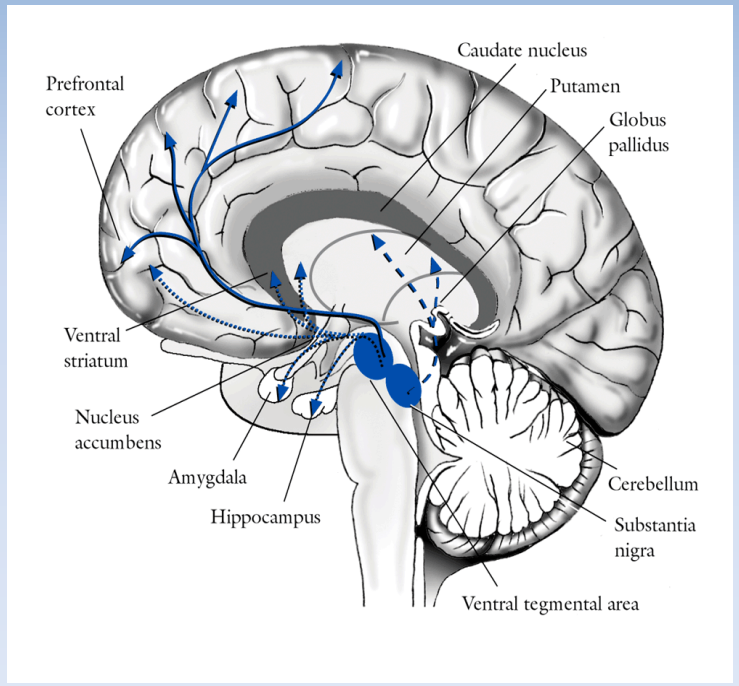
Brain Stimulation: Past, Present and Future

Session on Modelling and imaging of the brain effects of stimulation: Combining TMS/PET

OBJECTIVES

- To describe different PET radiotracers used to image the dopaminergic system.
- To learn about the effects of brain stimulation on the dopaminergic system.
- To describe TMS effects on brain functions and diseases.

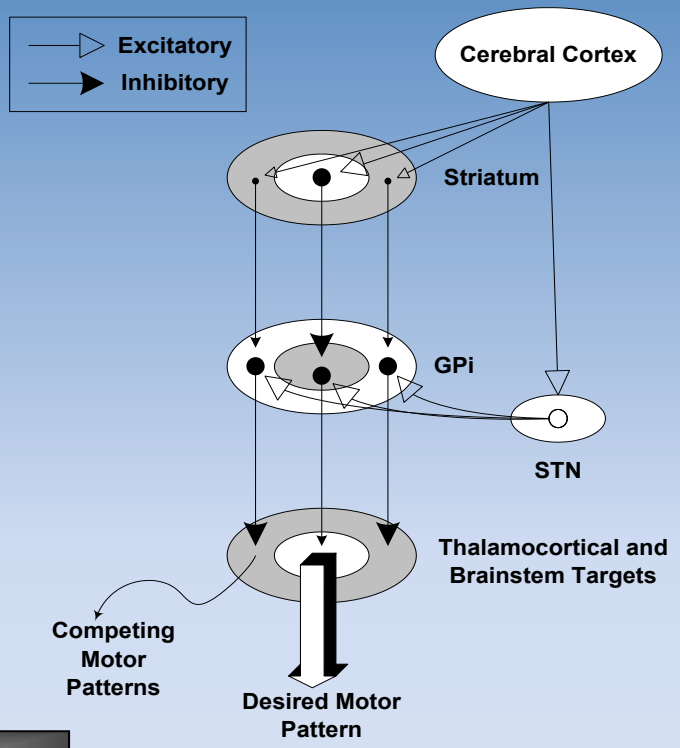




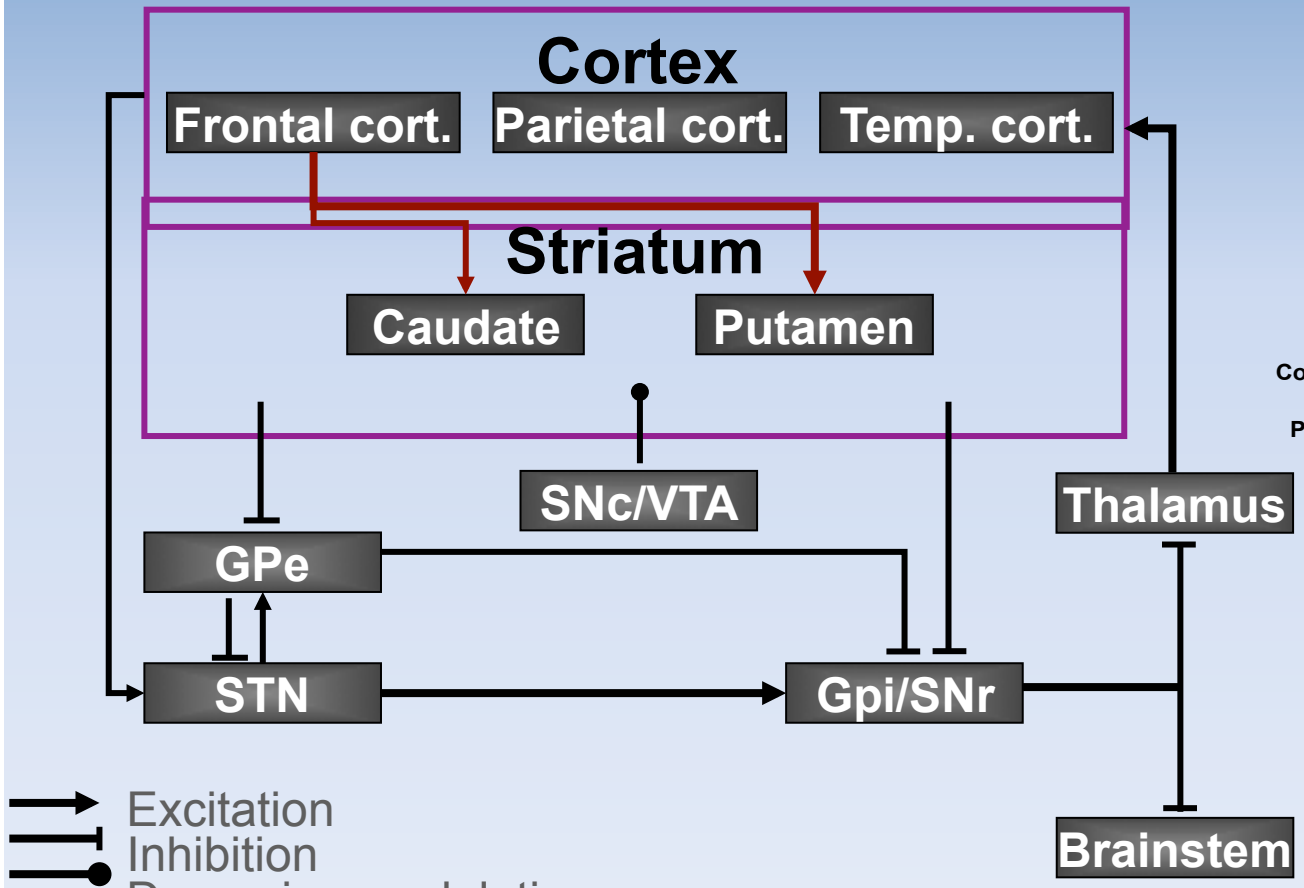
Parkinson's disease **Huntington's disease**

Depression **Schizophrenia** **Drug/Behavioral addiction**

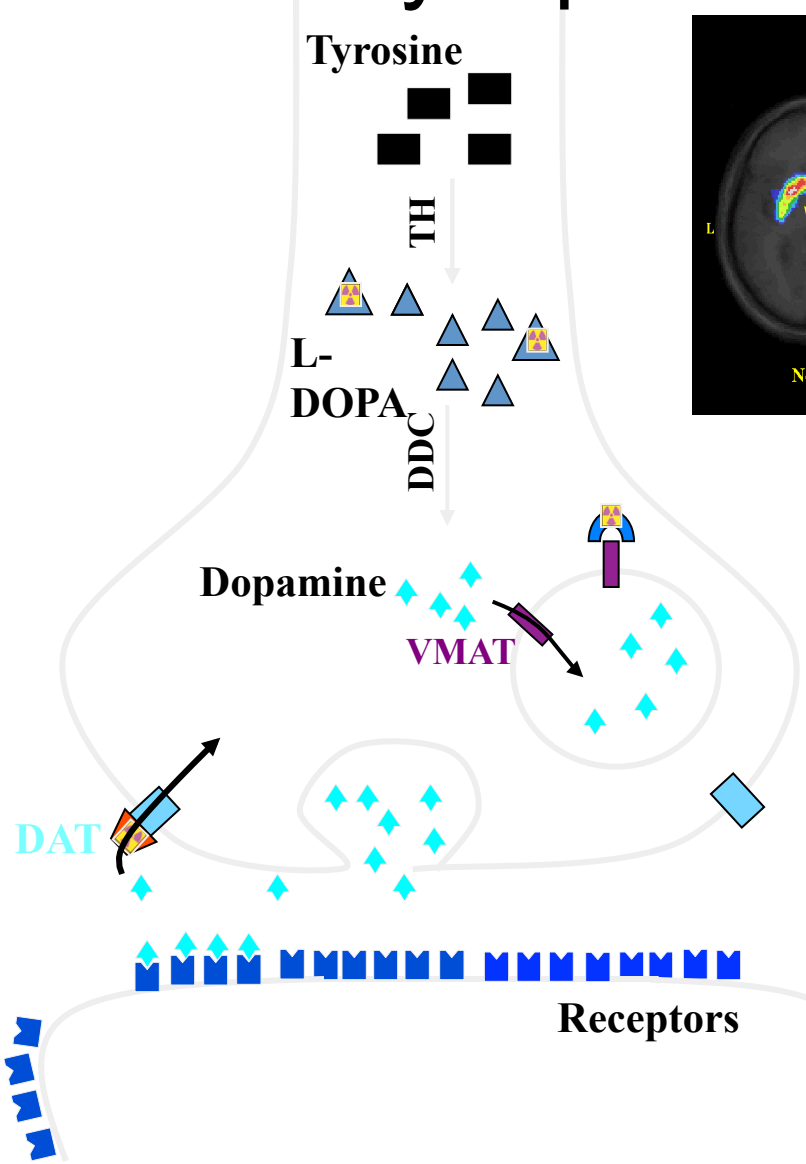
Cortical-Striatal Connection

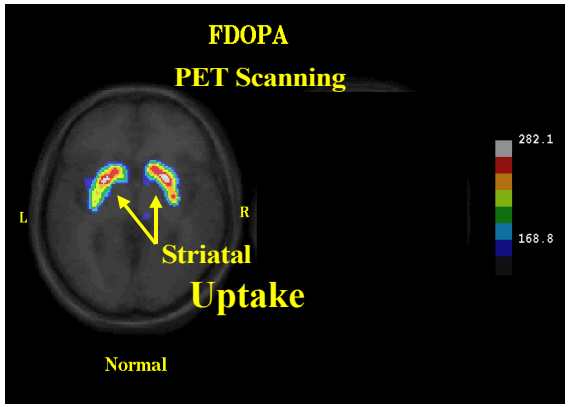


Mink. Prog. Neurobiol., 1996
Mink. Arch. Neurol., 2003

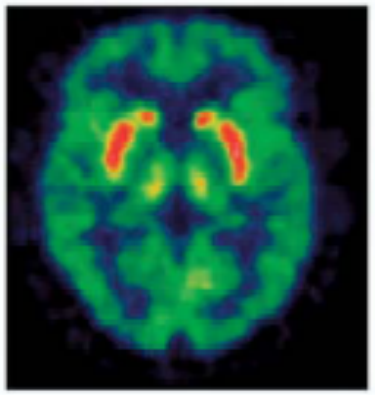


Dopaminergic ligands: Pre-synaptic Imaging



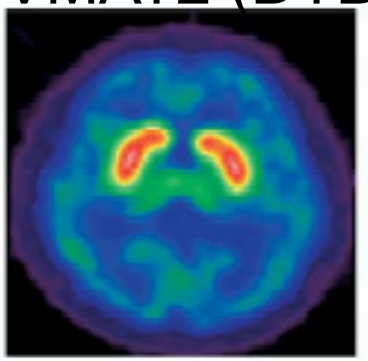


DAT (MP)



Normal

VMAT2 (DTBZ)



Normal

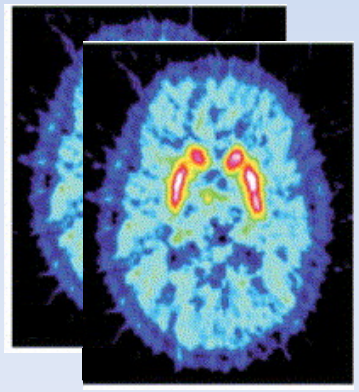
Dopamine D2/D3 Receptor Imaging Agent in Striatum

[^{11}C]raclopride

[^{123}I]IBZM

PET agent
Affinity (KD) = 1.1nM

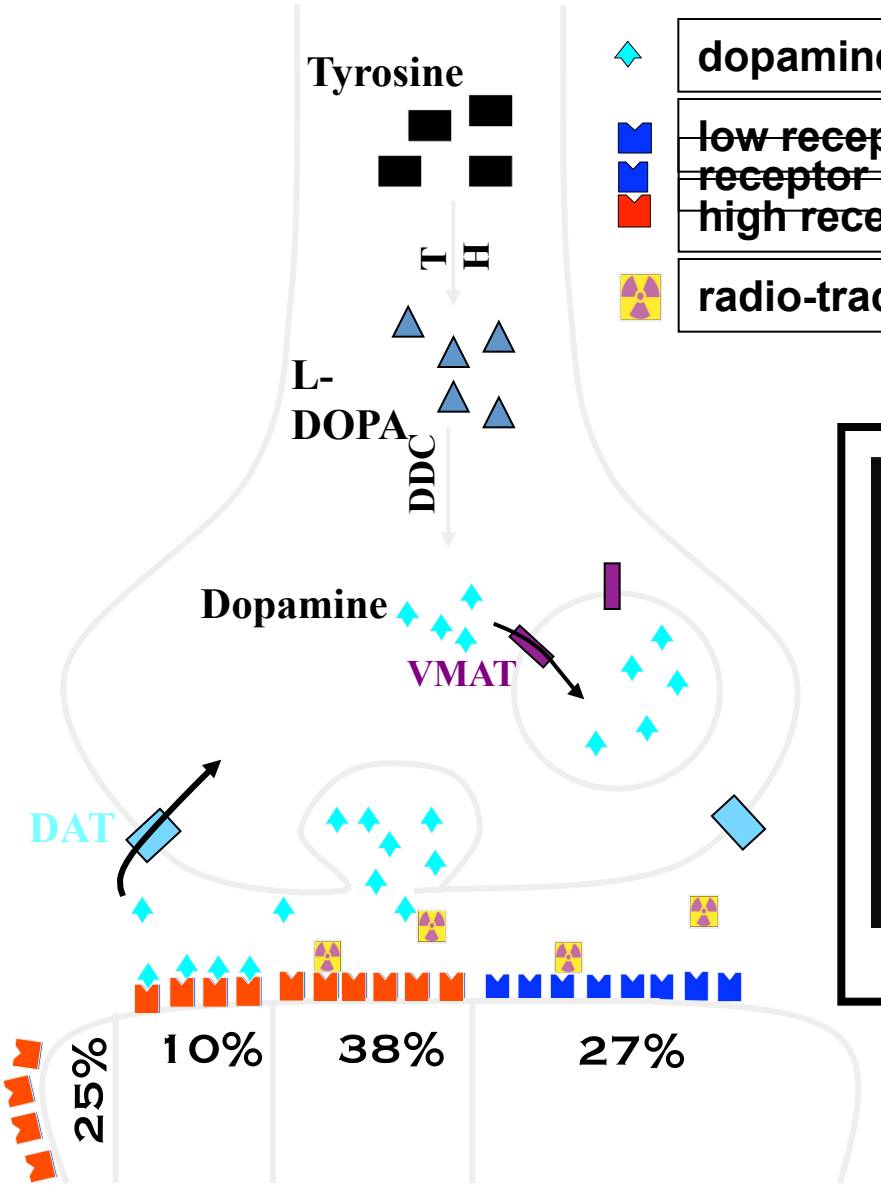
SPECT agent
Affinity (KD) = 0.4nM



Jucaite et al., 2005

Laruelle et al., 1997

Post-synaptic Imaging in PD



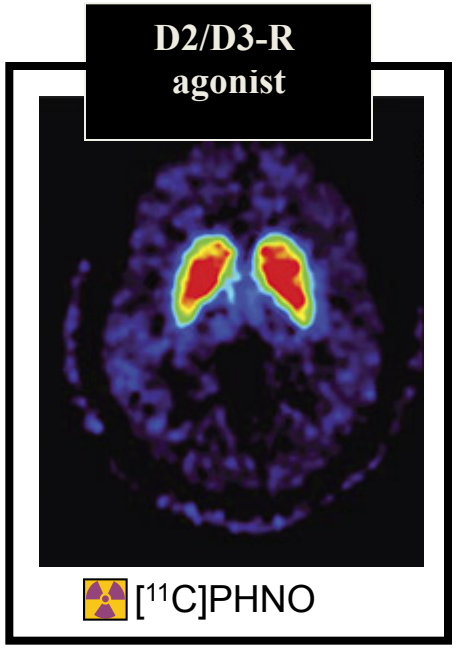
dopamine

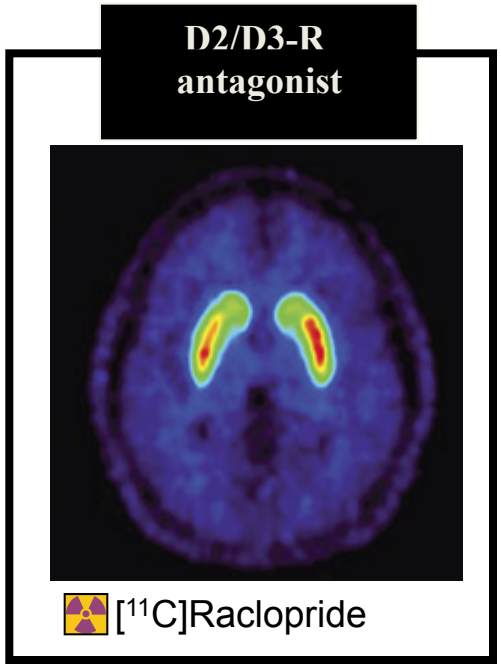
low receptor

receptor

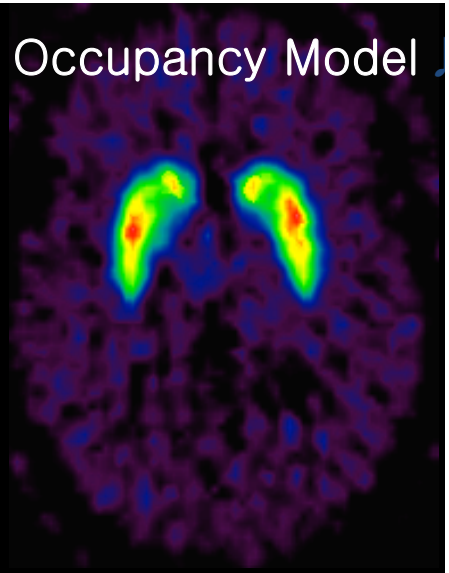
high receptor

radio-tracer





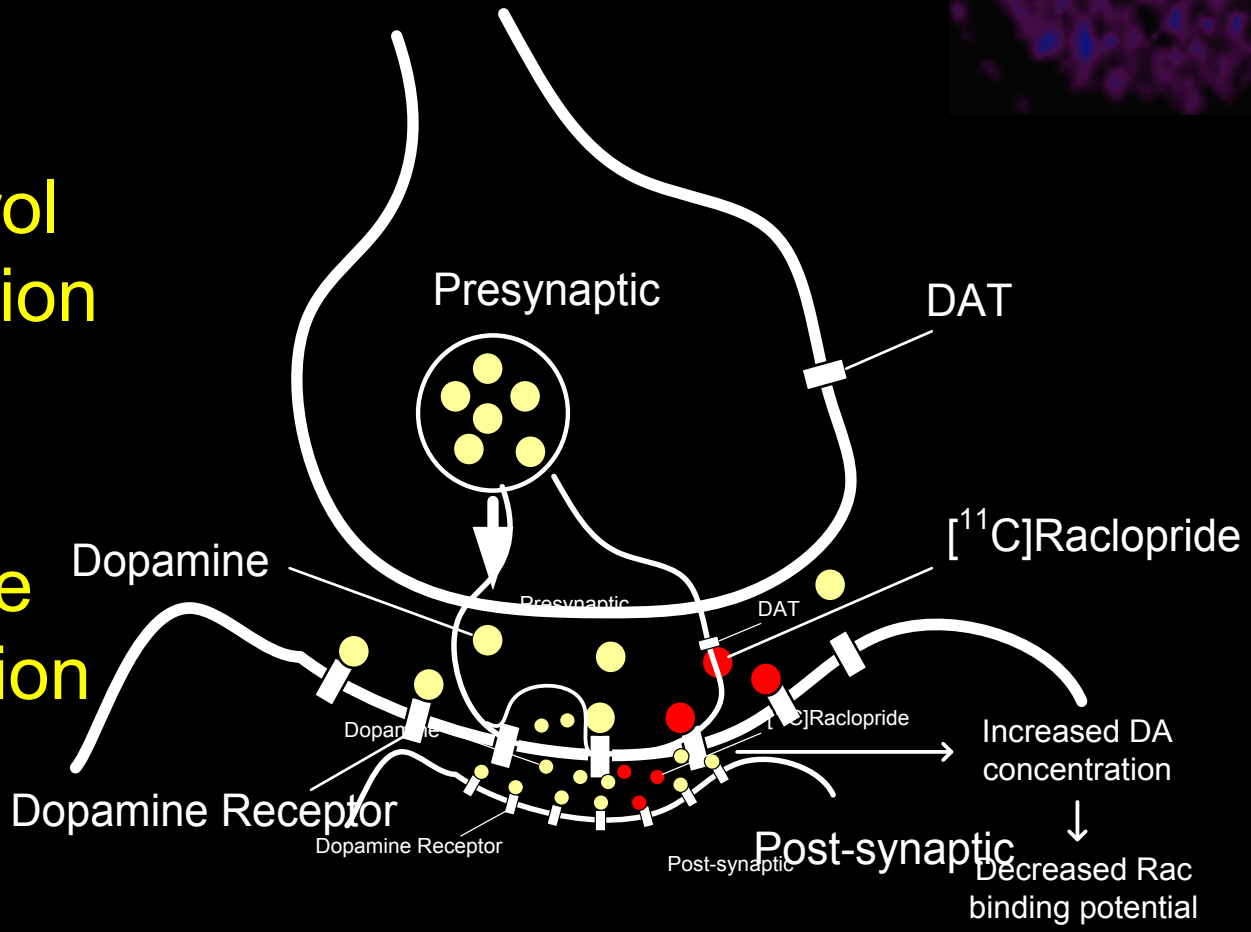
Displacement Studies: Release of dopamine



Control condition

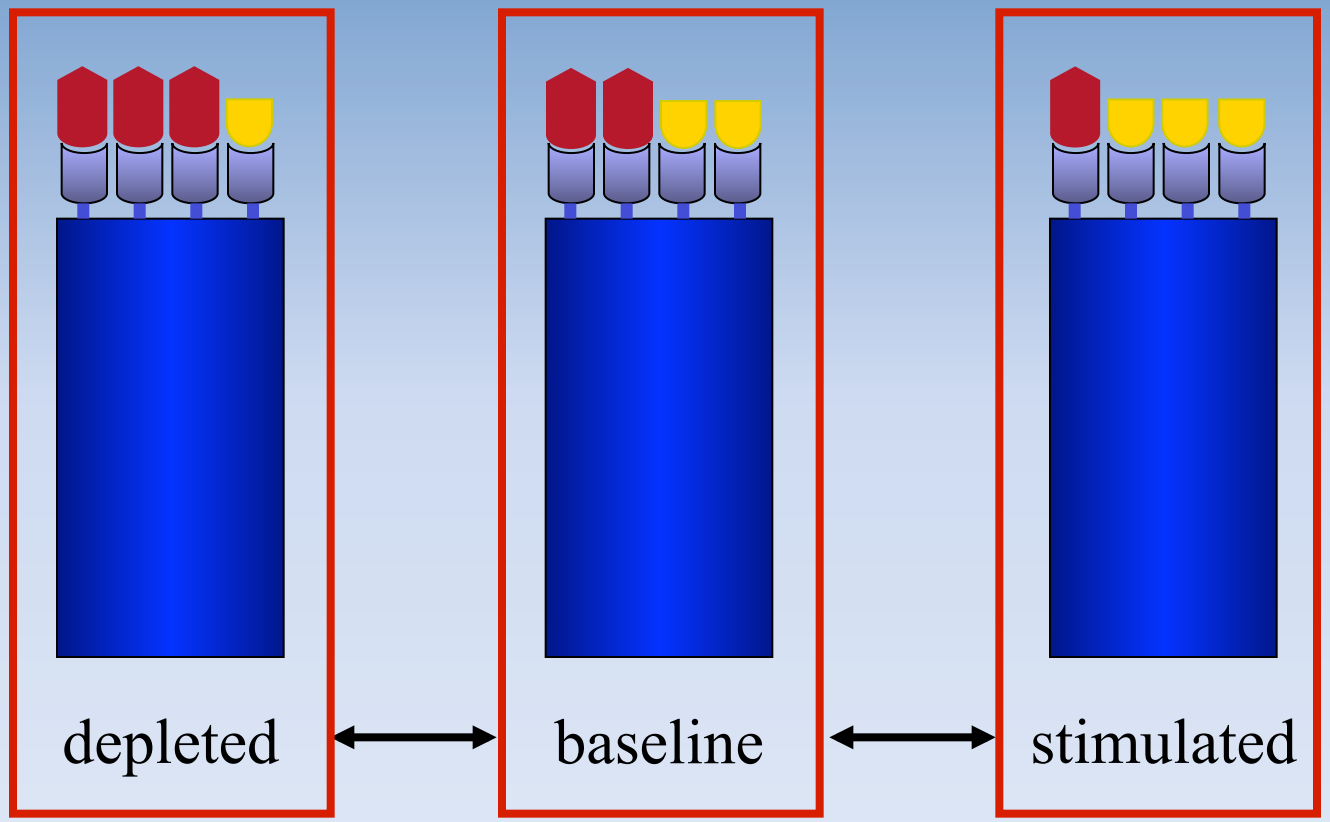
VS

Active condition

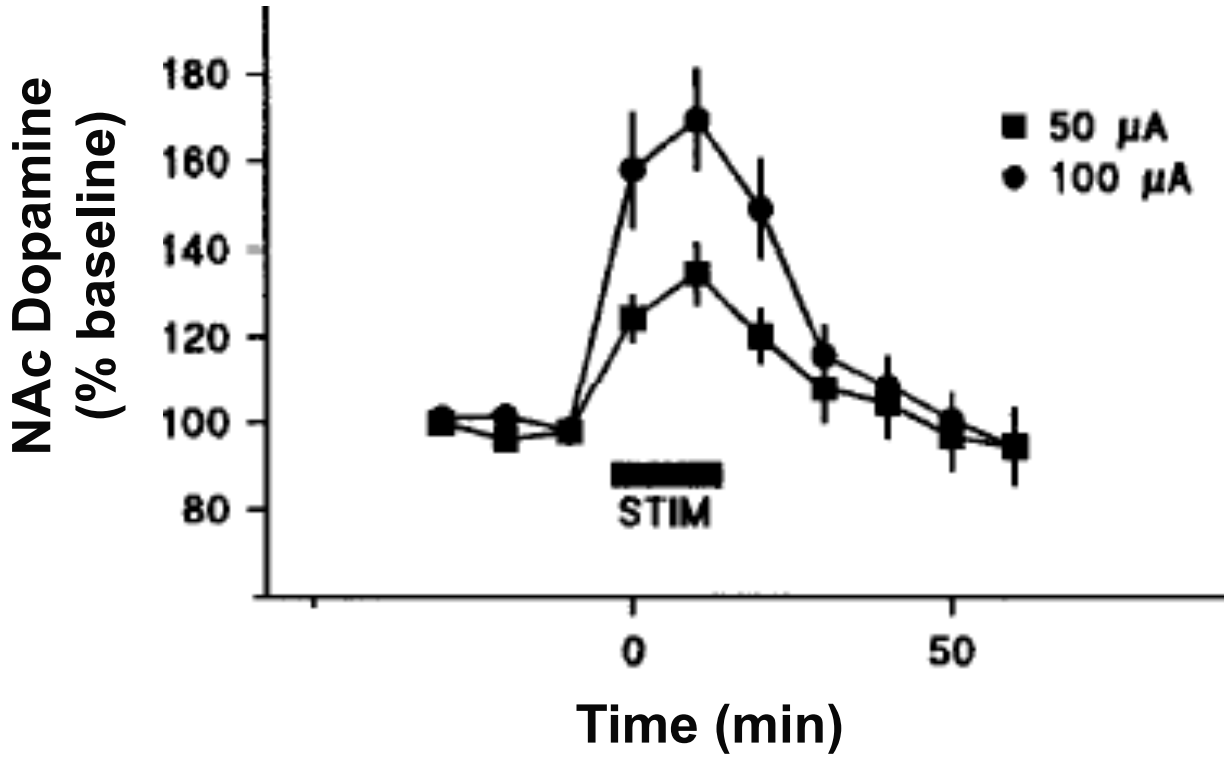


Laruelle, J Cereb Blood Flow Metab (2000)

Classical Occupancy Model



Effects of Electrical Stimulation of Prefrontal Cortex on Dopamine Release

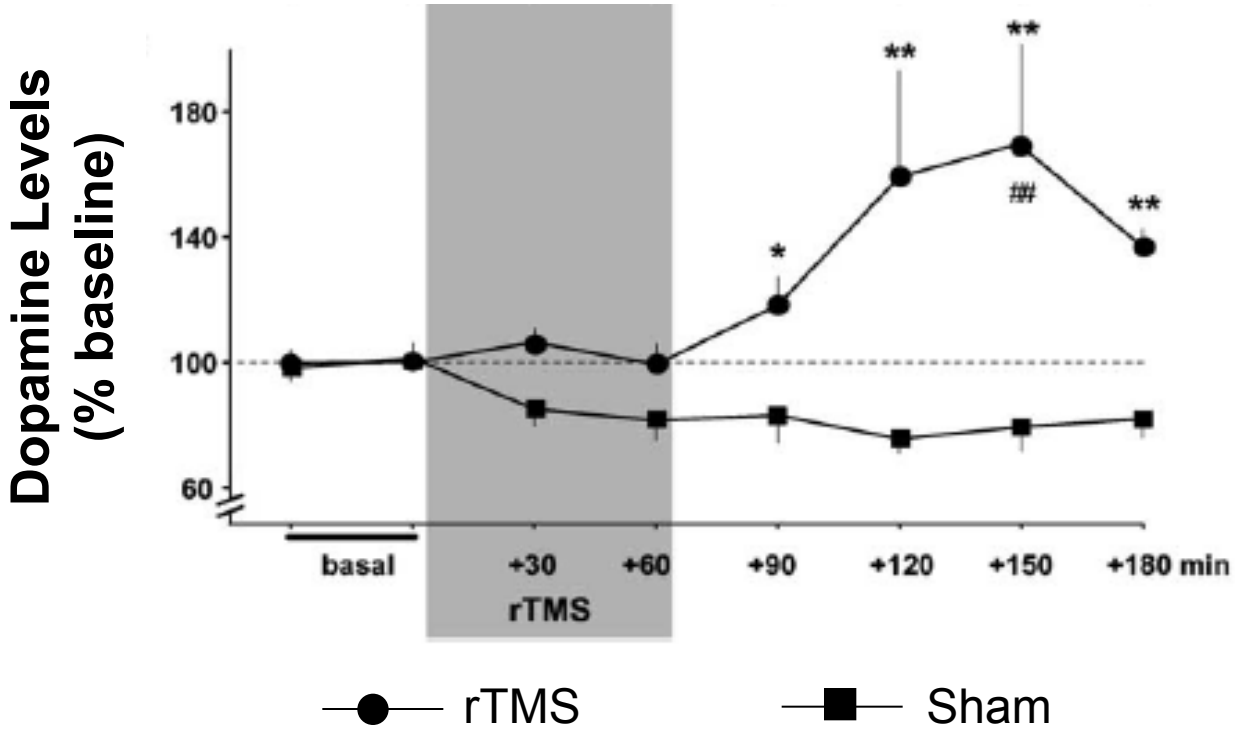


microdialysis experiments

Taber and Fibiger, J of Neuroscience,1995

rTMS Effect on Dopamine Release

Dorsal Striatum

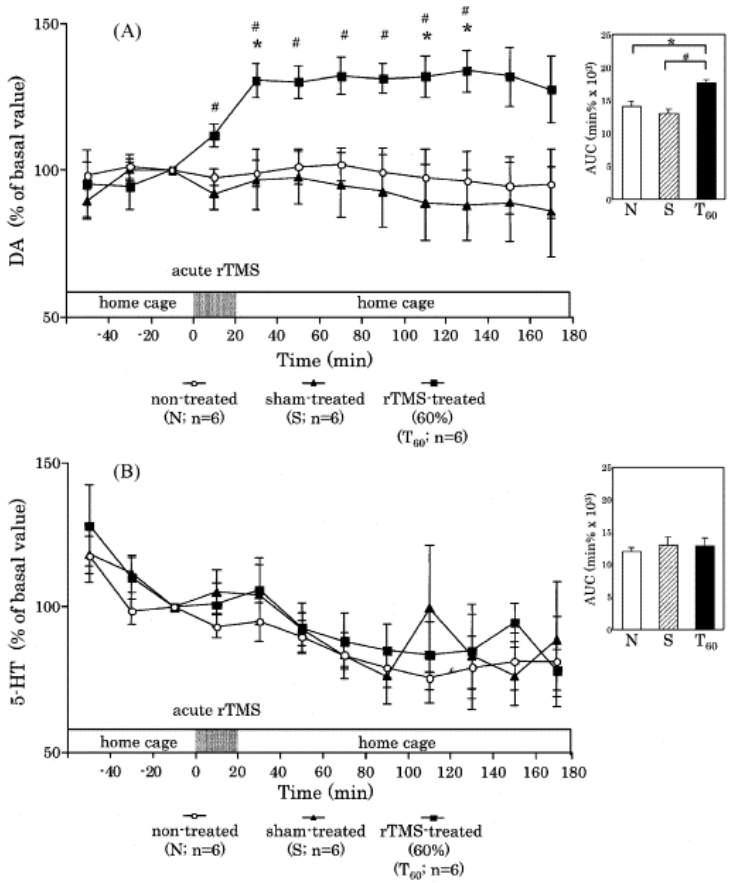


microdialysis experiments

Keck et al., Neuropharmacology, 2002

rTMS Effect on Dopamine Release

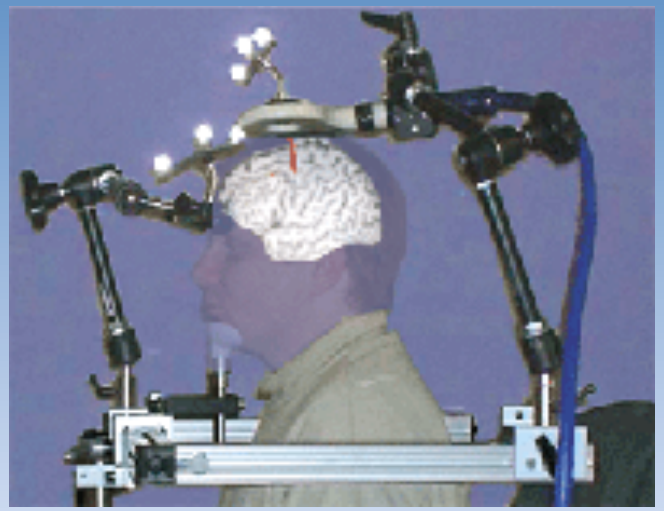
Dorsal Striatum

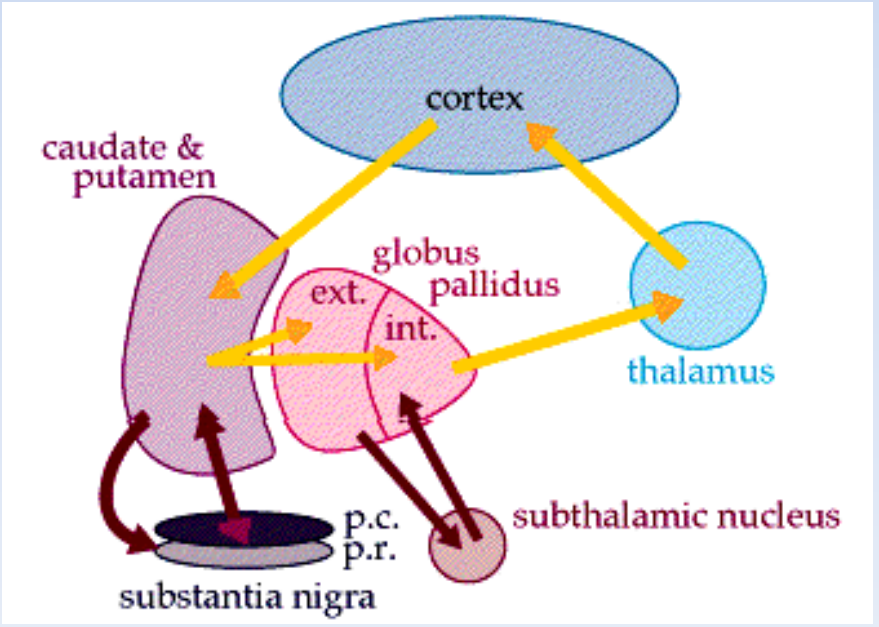


microdialysis experiments

Kanno et al. J. Neurol Sci. 2004

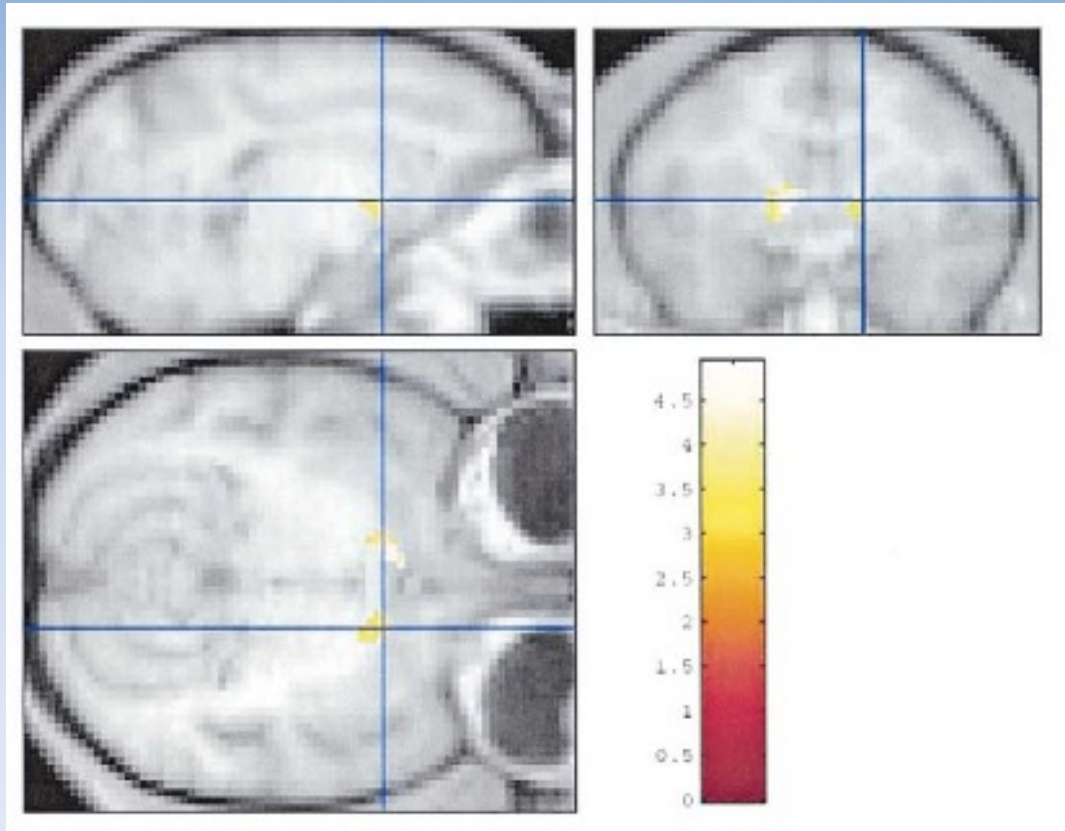
Neuro-receptor Imaging





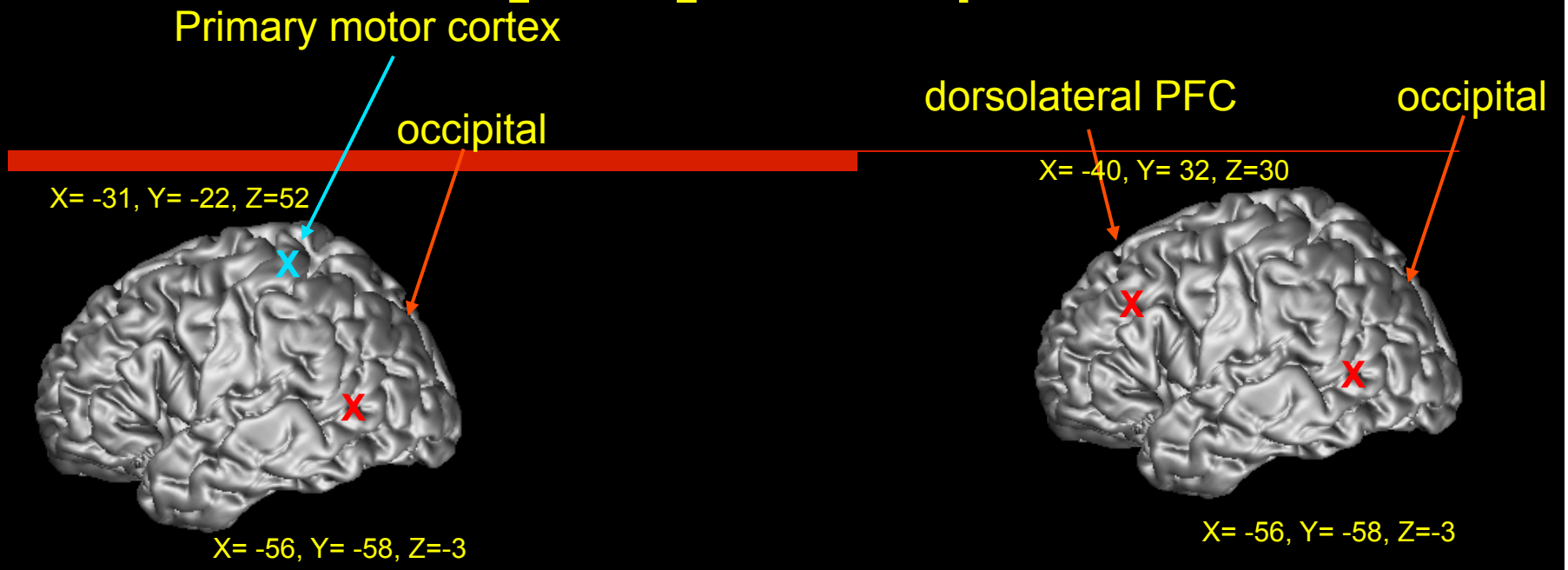
rTMS & Striatal Dopamine

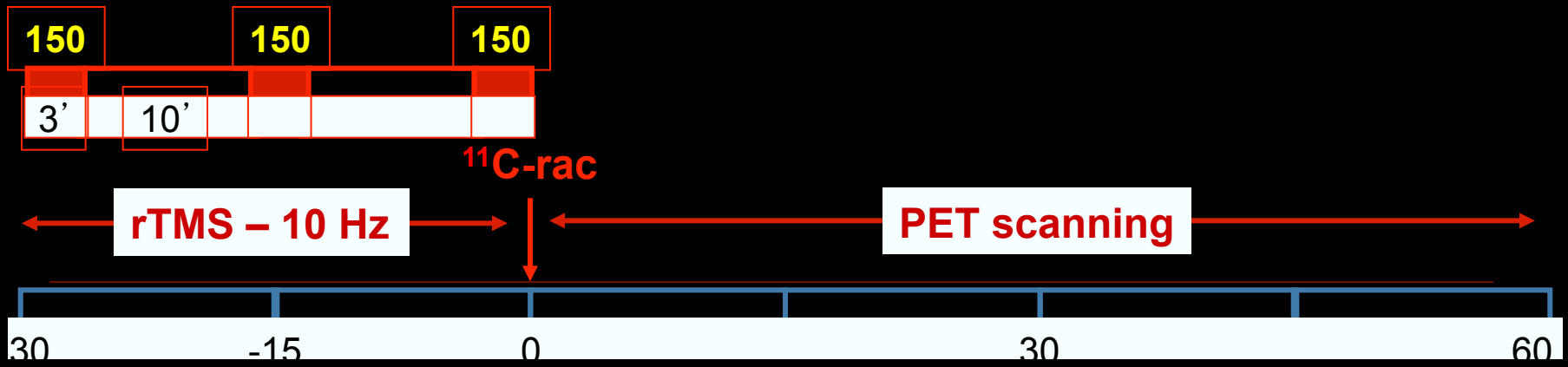
Macaque Monkeys



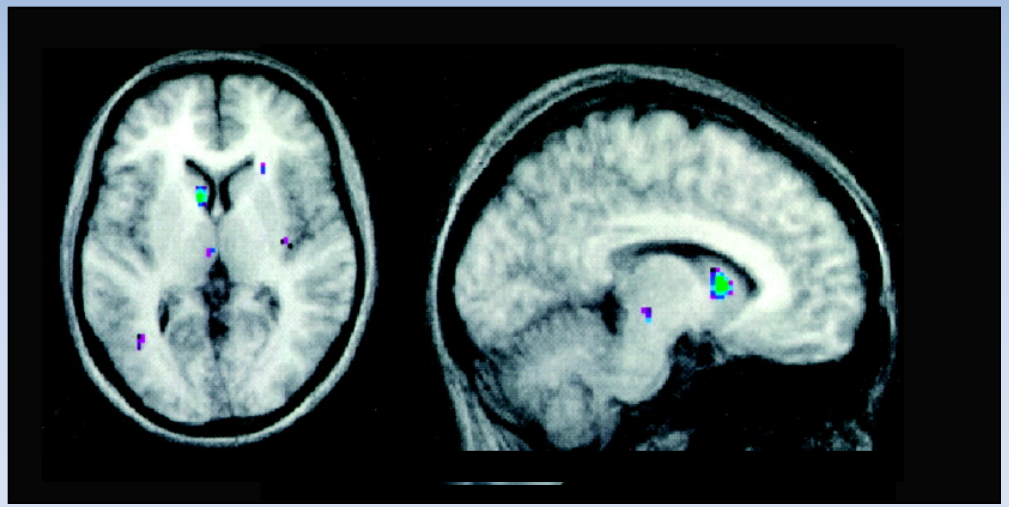
Ohnishi et al., 2004

TMS and [^{11}C] raclopride PET



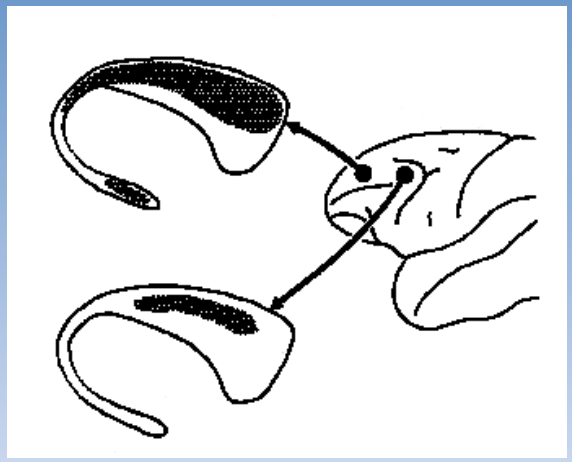


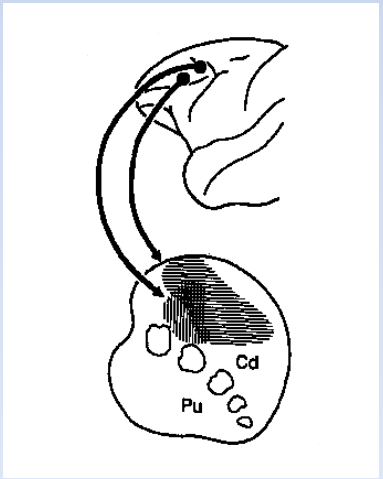
rTMS & Striatal Dopamine
-Stimulation of DLPFC-



Mean Δ%BP = -7.3%

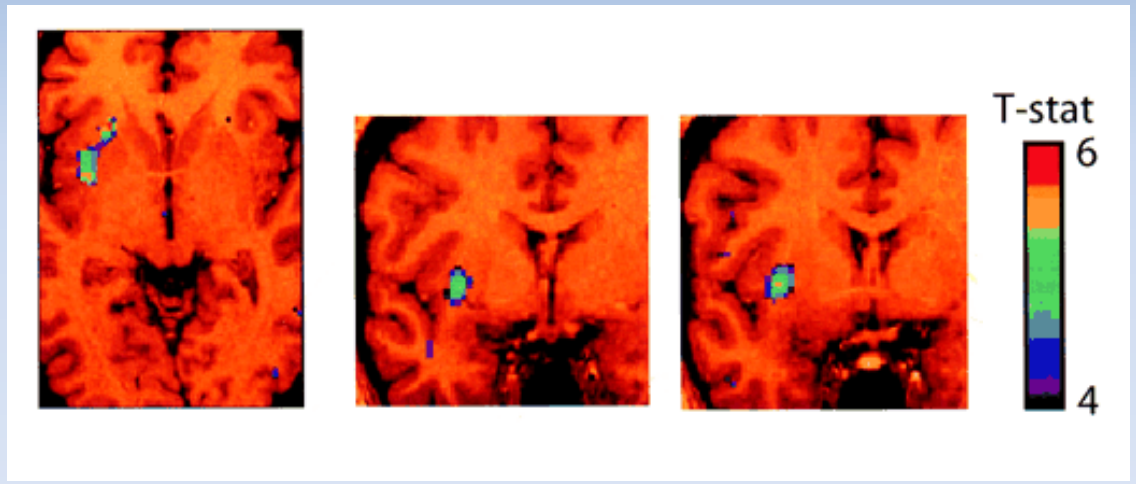
Strafella et al., J of Neuroscience, 2001





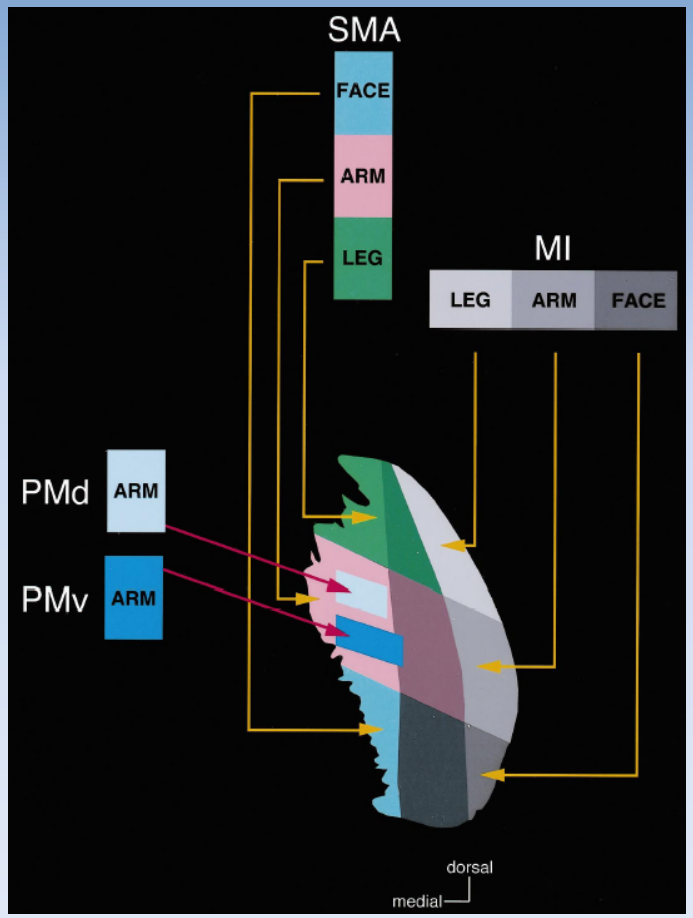
Yeterian and Pandya
J. Comp. Neurol. 1991

rTMS & Striatal Dopamine
-Stimulation of motor cortex-



Mean Δ%BP = -9.5%

Strafella et al., Brain, 2003



Takada et al., Exp Brain Res. 1998

Striatal dopaminergic effects
TMS versus amphetamine challenge

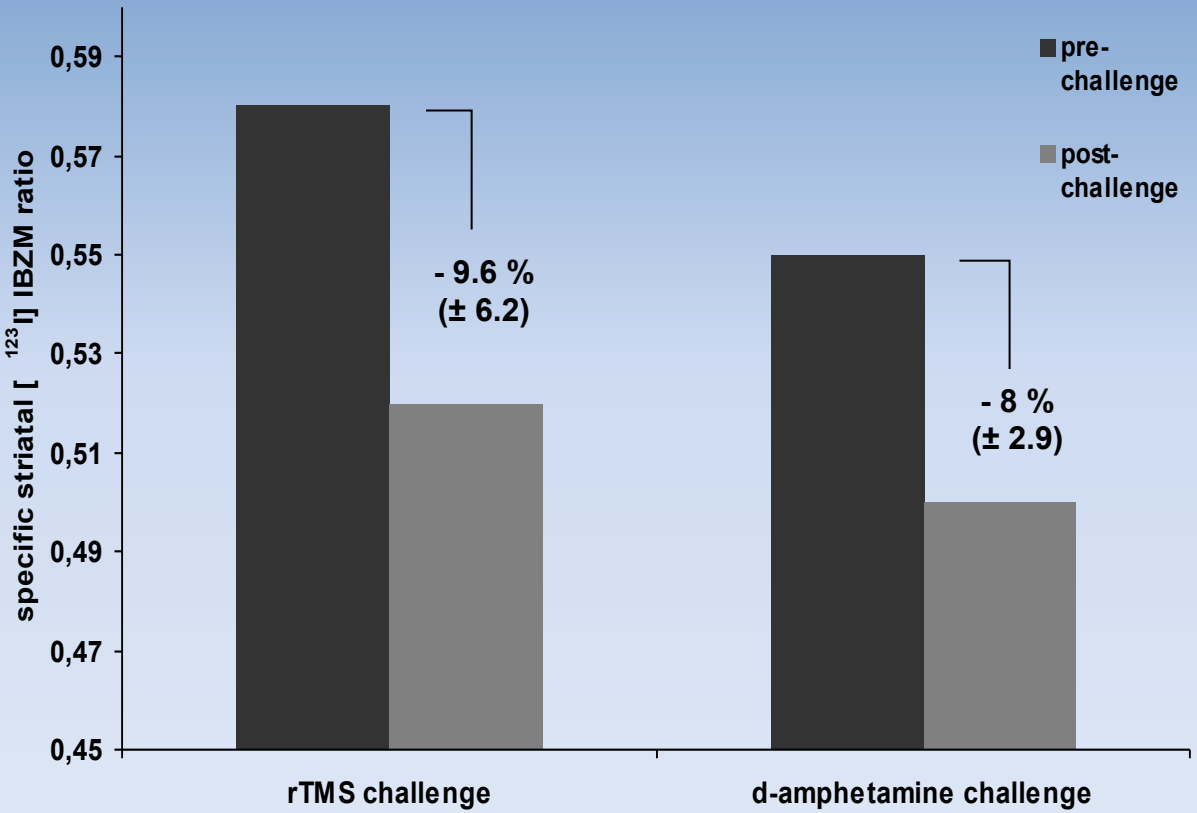
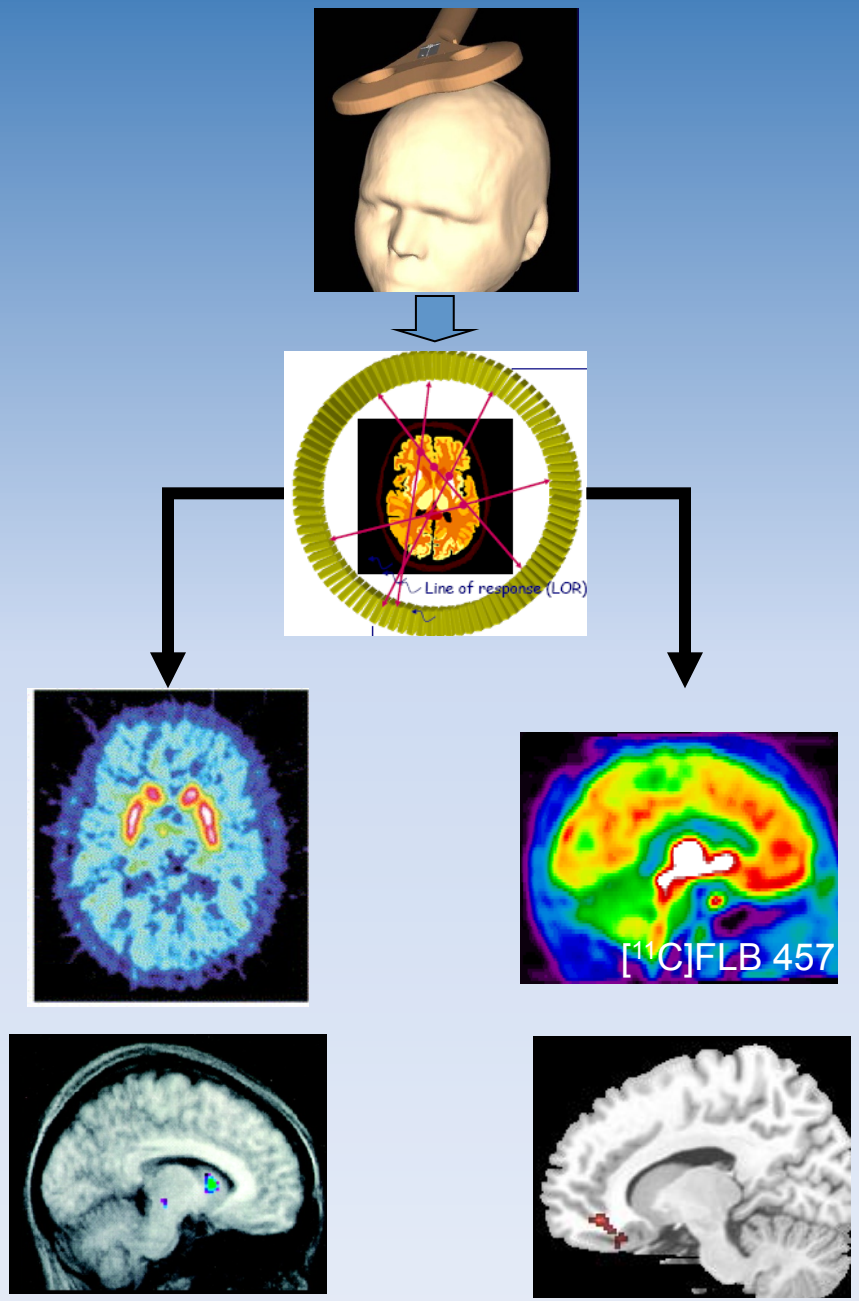


Figure: Mean specific striatal IBZM-binding (striatal-occipital/occipital) before and after rTMS (left) and d-amphetamine (right) challenge.

Pogarell et al., Psychiatry Res , 2007

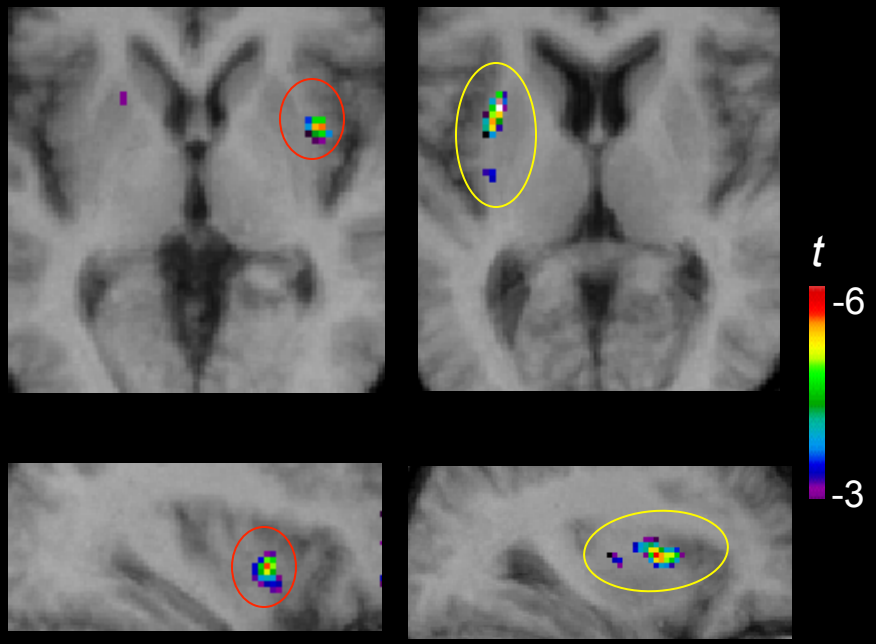


- *rTMS effect on behaviors and possible clinical relevance.*

TMS-induced release of dopamine in PD

Reductions [^{11}C] raclopride BP

Asymptomatic Hemisp. Symptomatic Hemisp.

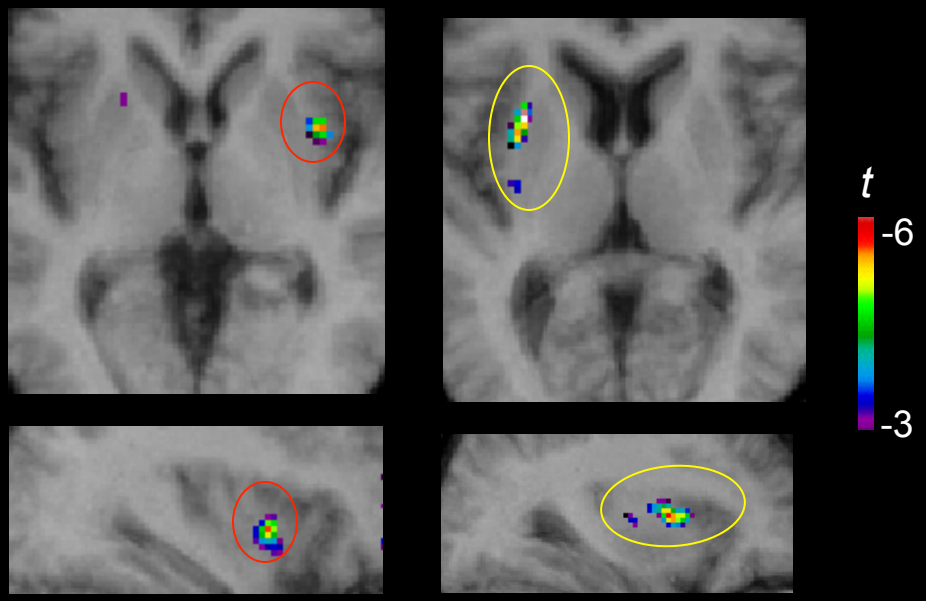


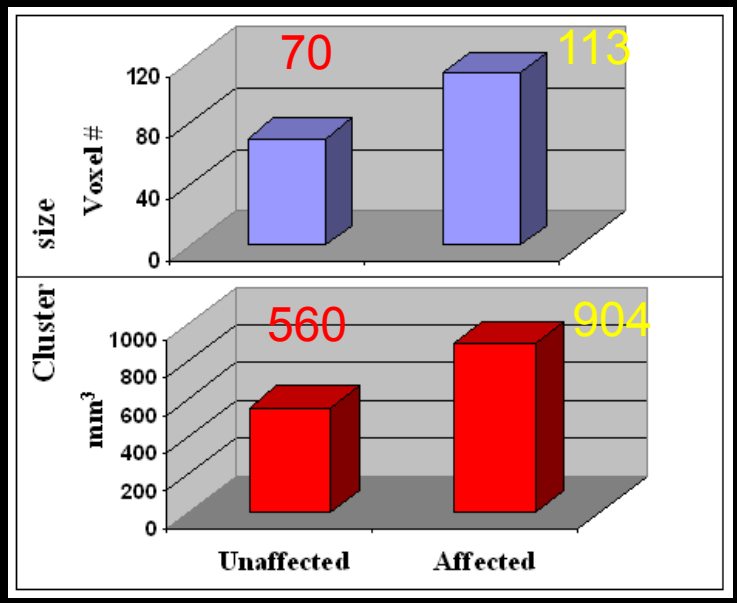
- Reduction in [^{11}C] BP in ipsilateral putamen
- 12.9 % reduction in asymptomatic hemisphere
- 9.45 % reduction in symptomatic hemisphere

Strafella et al., EJN 2005

Reduction [^{11}C] raclopride BP

Asymptomatic Hemisp. Symptomatic Hemisp.





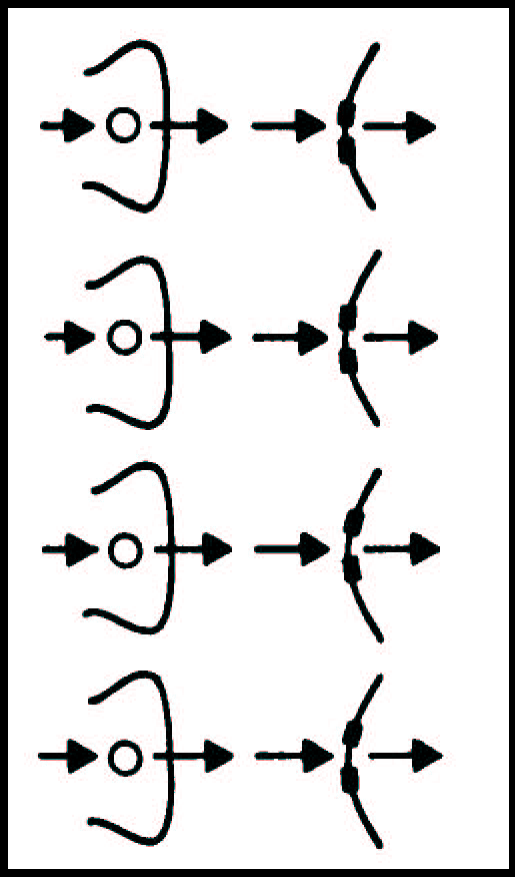
- 61.4 % increase in cluster size

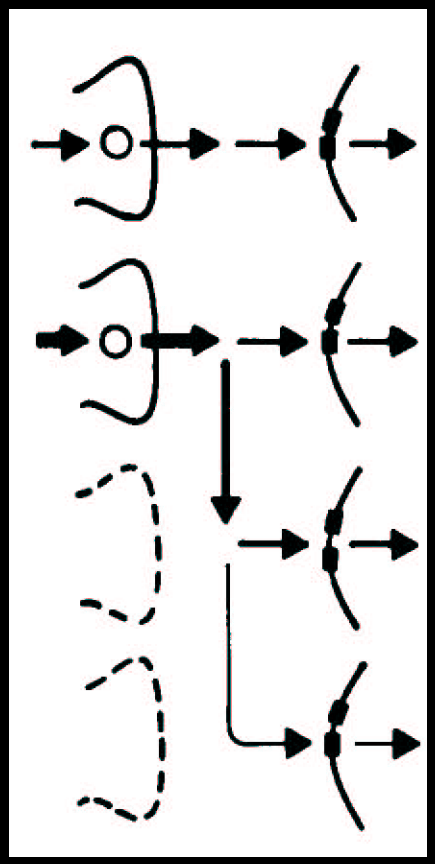
Strafella et al., EJN 2005

Loss of functional segregation

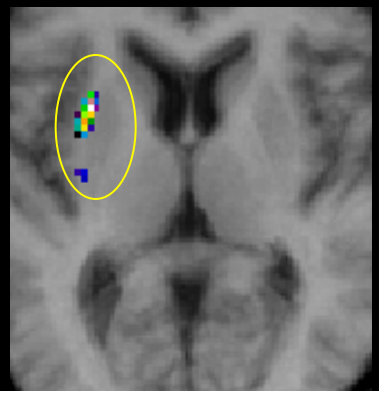
Normal

Nigrostriatal degeneration





- Because of loss of re-uptake sites, released dopamine diffuses out to more distant regions of the receptor population in the dopamine-denervated striatum > loss of functional segregation

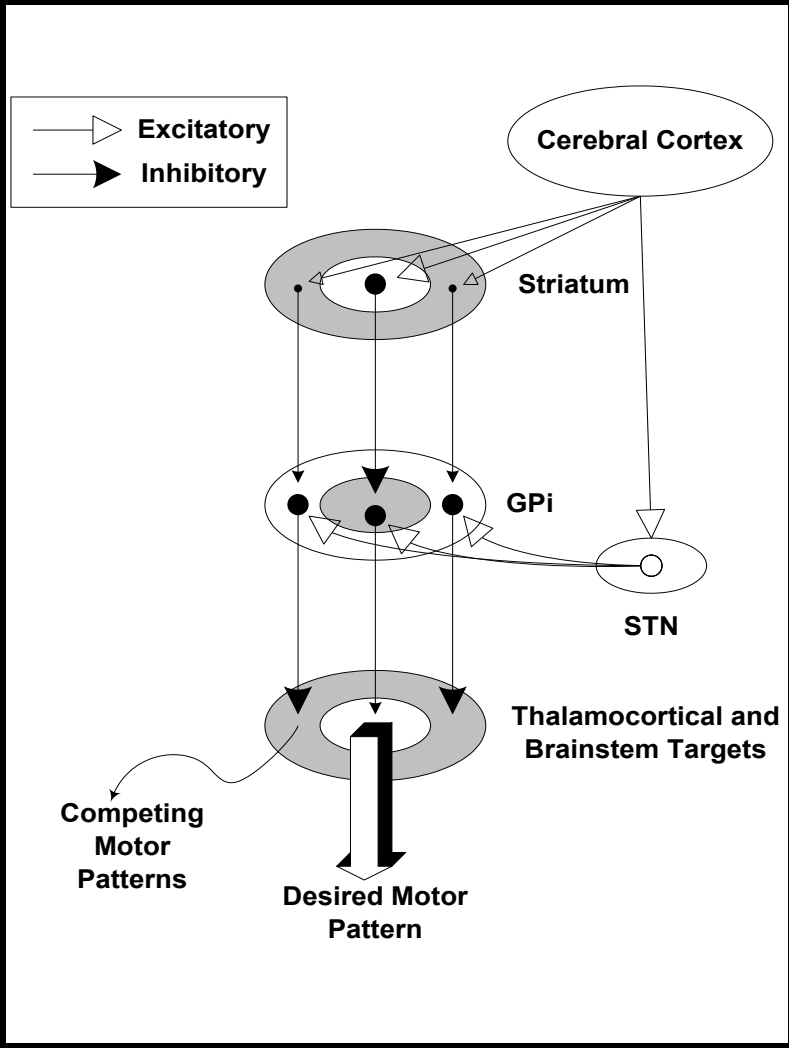


Zigmond et al. TINS 1990

Functional implications for models of basal ganglia function in PD

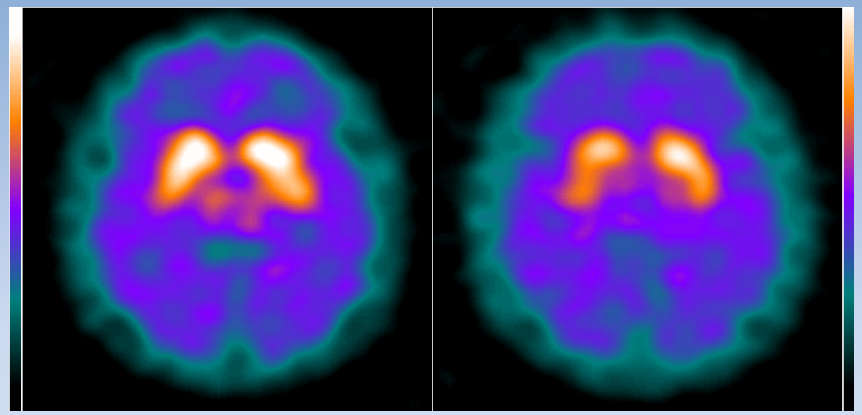
- The neuroanatomical arrangement of the cortico-striatal system in a center-surround inhibitory pattern is thought to facilitate activity in cortico-striatal loops involved in the current task with concomitant suppression of competing motor networks.

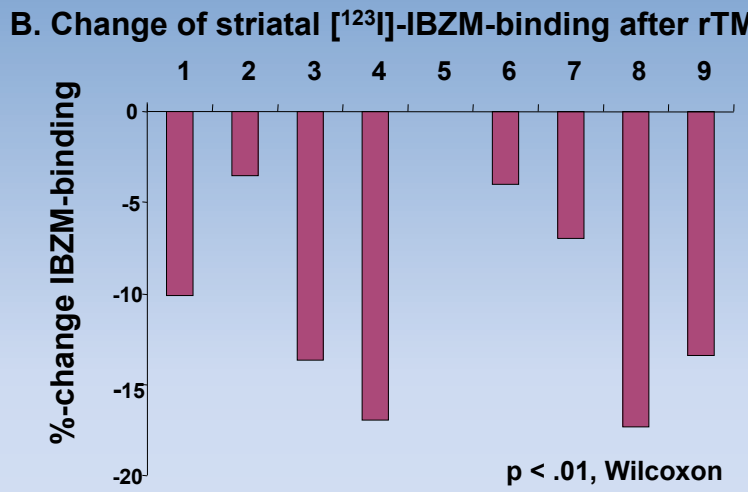
- The loss of functional segregation may favor the de-arrangement of the selective facilitation/surround inhibition pattern leading to impaired inhibition of competing motor patterns.

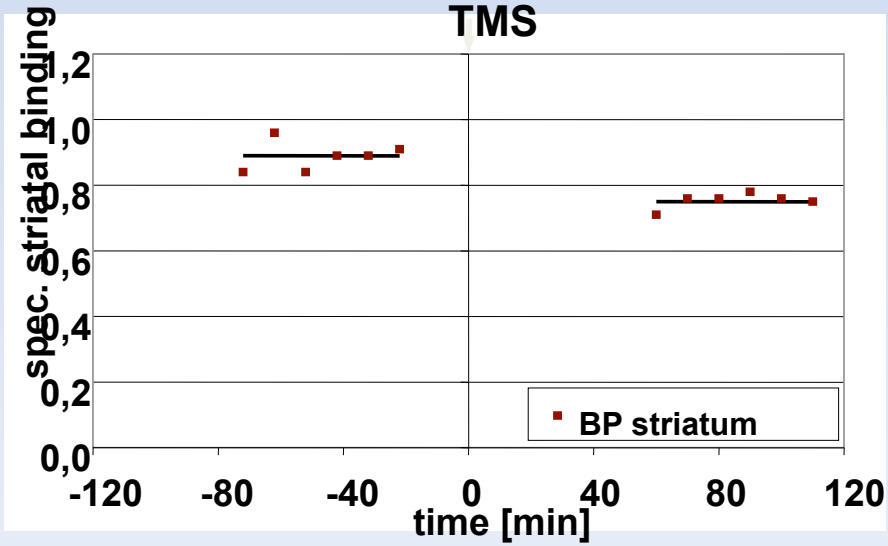


Mink. Prog. Neurobiol., 1996.
Mink. Arch. Neurol., 2003.

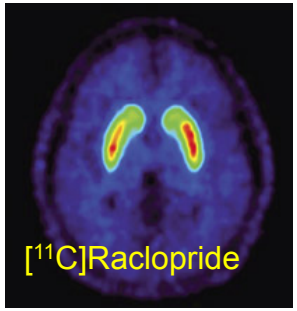
Reduction of [^{123}I]-IBZM binding following left prefrontal rTMS in major depression

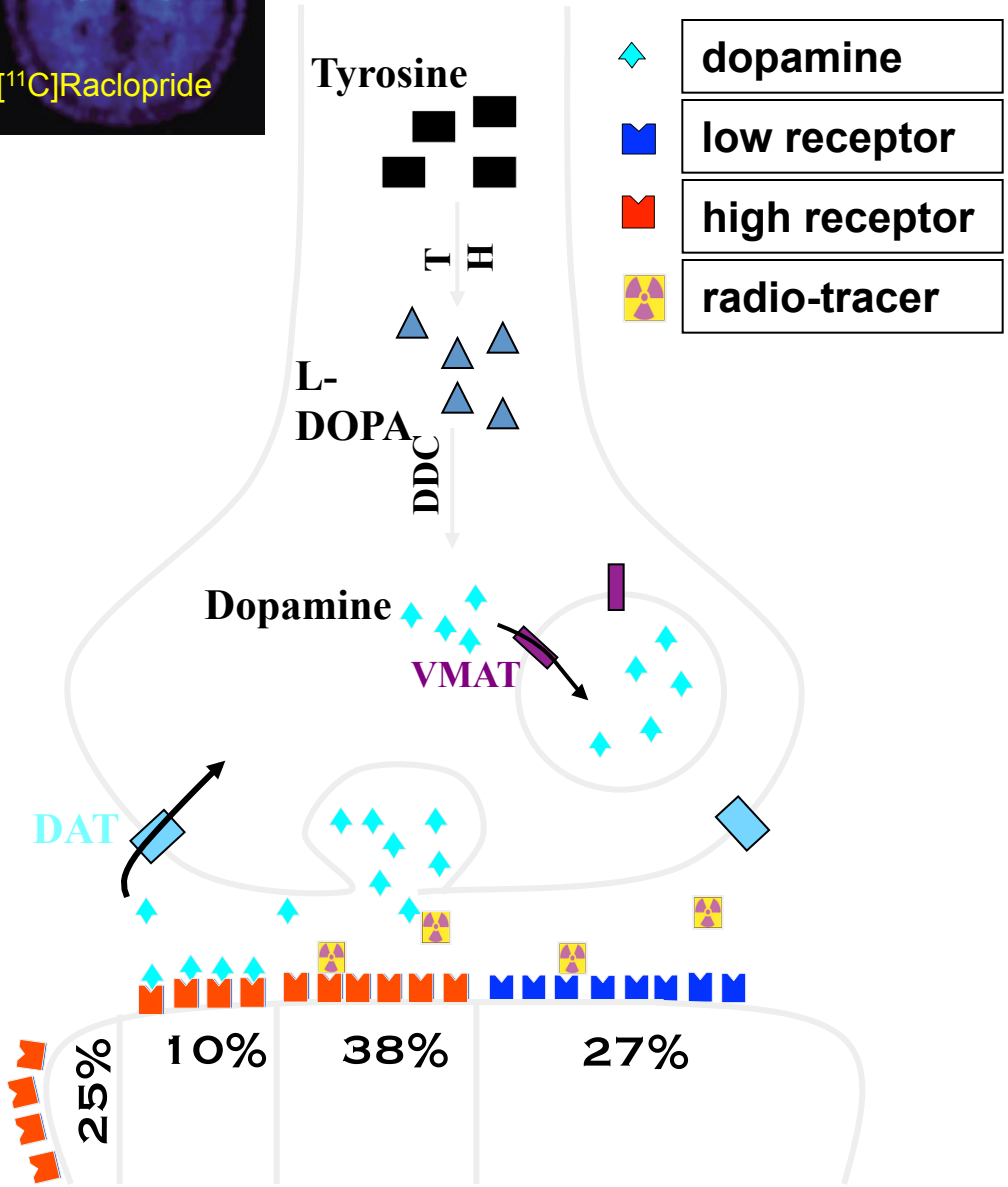






Pogarell et al. *J Psychiatr Res* 2006





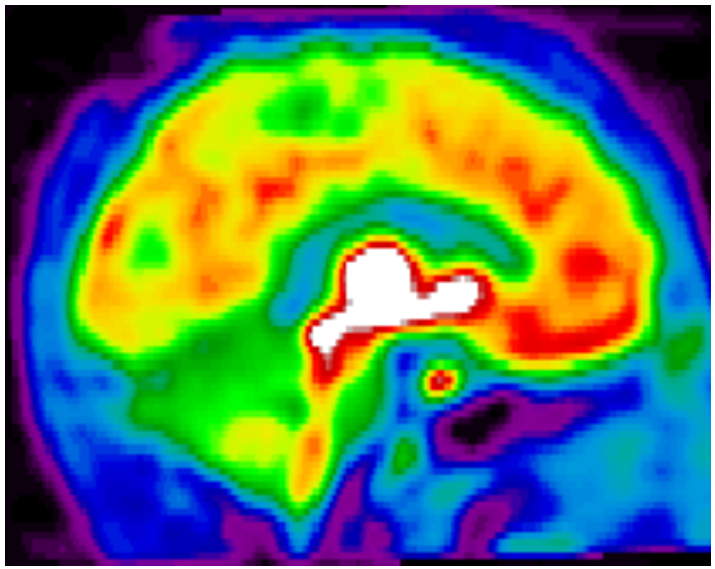
dopamine

low receptor

high receptor

radio-tracer

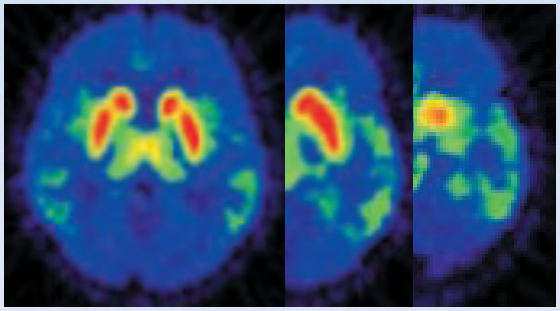
D2 antagonist



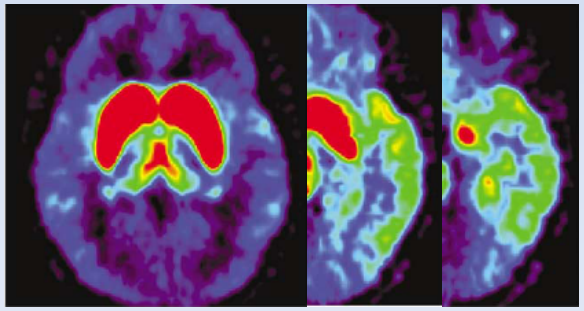
[11C]FLB 457

Dopamine D2/D3 Receptor Imaging Agent in Extrastriatal Region

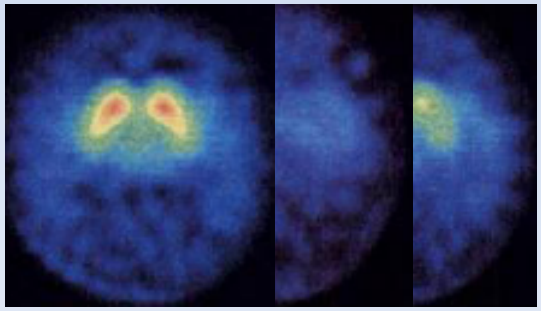
[^{11}C]FLB 457	[^{18}F]Fallypride	[^{123}I]Epidepride
PET agent	PET agent	SPECT agent
Affinity (Kd) = 20pM	Affinity (Kd) = 33pM	Affinity (Kd) = 24pM



Vilkman et al., 2007



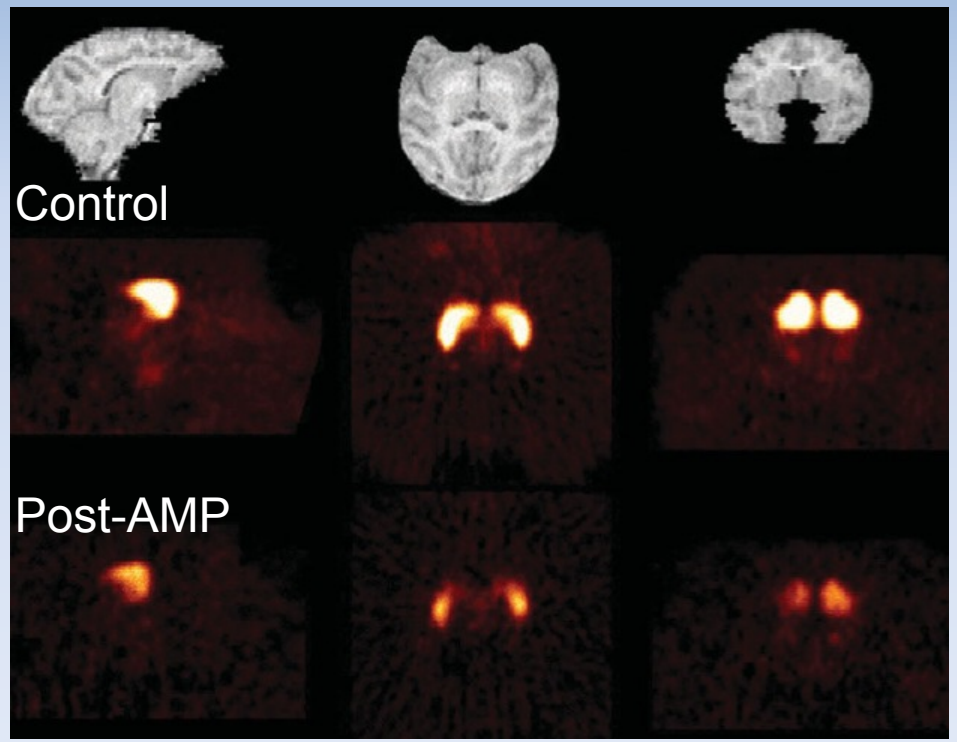
Riccardi et al., 2006



Varrone et al., 2000

Effect of Amphetamine on DA

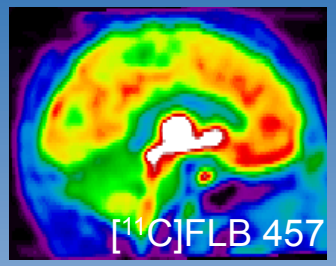
Baboon monkey n=7
[^{18}F]Fallypride



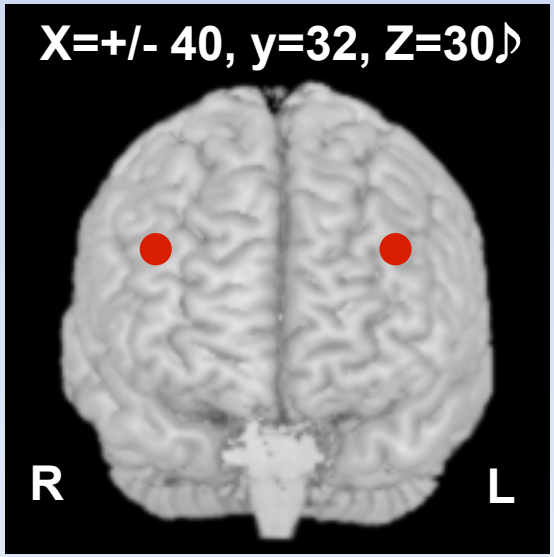
	Con.	Post-AMP	Δ%BP
striatum	22.36	11.31	-49
thalamus	1.51	1.14	-25
midbrain	0.91	0.65	-28
cingulate	0.31	0.18	-41
hippocampus	1.33	0.84	-36

Slifstein et al., Synapse, 2004

Effect of DLPFC rTMS on extrastriatal areas: [^{11}C]FLB457 PET Study



Target Area (DLPFC)

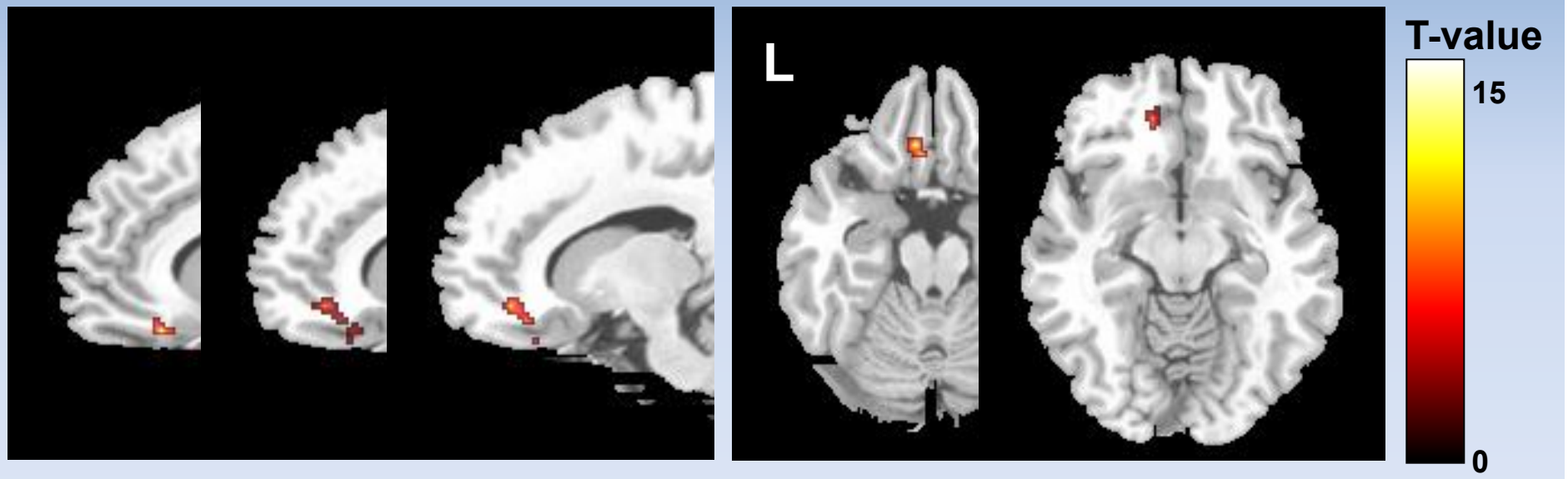


- MagStim Rapid^2/8-shape coil
  - Total stimulation block :5 blocks
  - Total stimulation pulse: 750 pulse
    - 15 1s 10Hz (100% RMT)
      - 10 sec inter train interval

- Siemens Biograph HiRez XVI PET/CT scanner
- 30 frames

Cho and Strafella 2009

Decrease of Cortical [^{11}C]FLB 457 BP following Left DLPFC rTMS

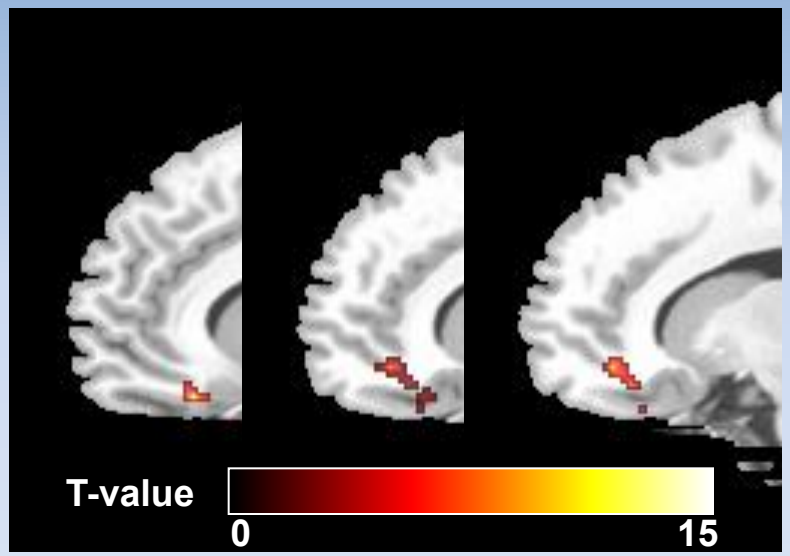


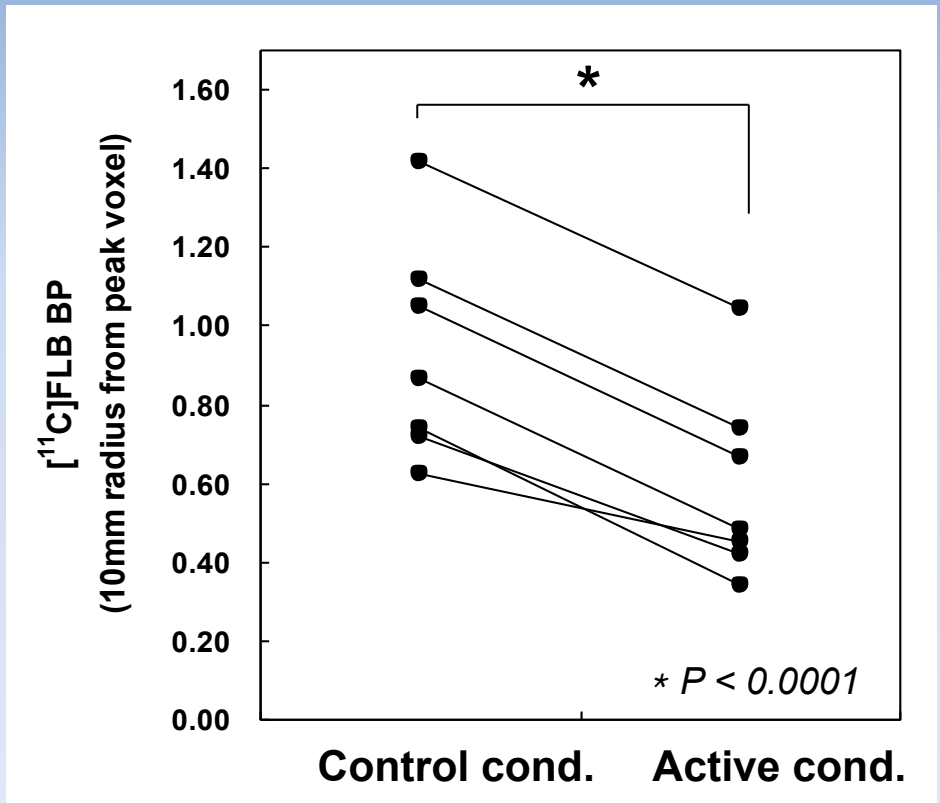
$P < 0.001$, k=20

Cho and Strafella 2009

Decrease of Cortical [^{11}C]FLB 457 BP following the Left DLPFC rTMS

-Individual BP in peak area-



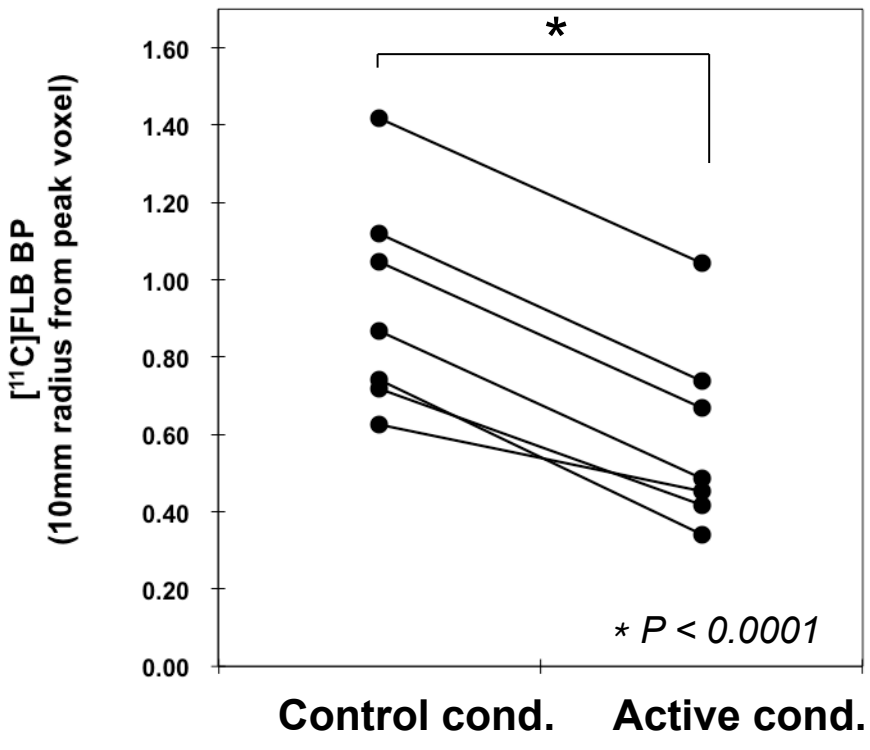


Cho and Strafella 2009

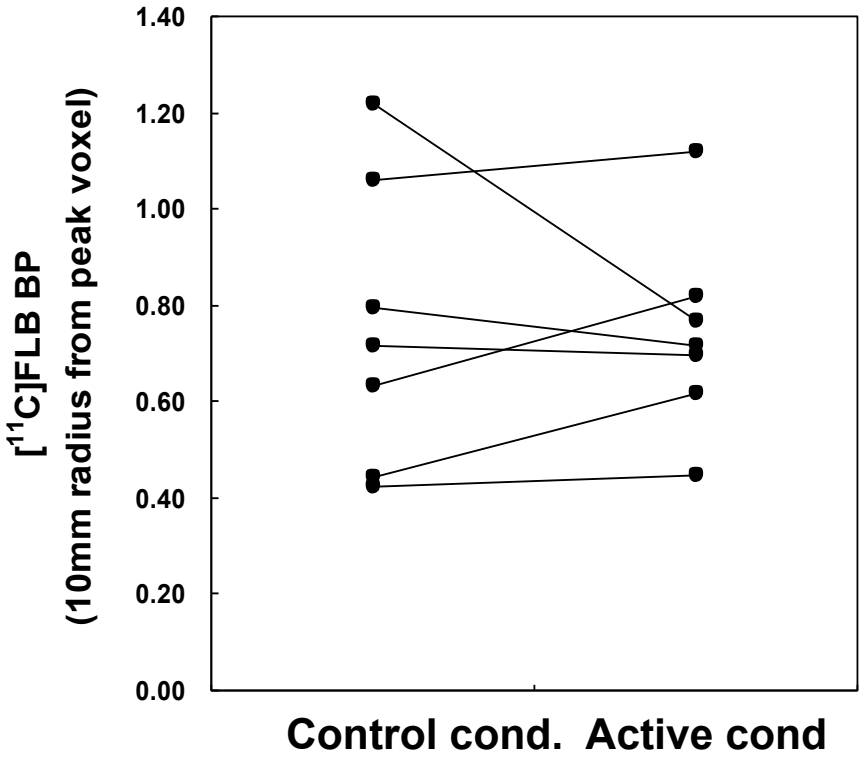
[11C]FLB 457 BP after the Left DLPFC rTMS

[11C]FLB 457 BP after the Right DLPFC rTMS

Left ACC



Right ACC



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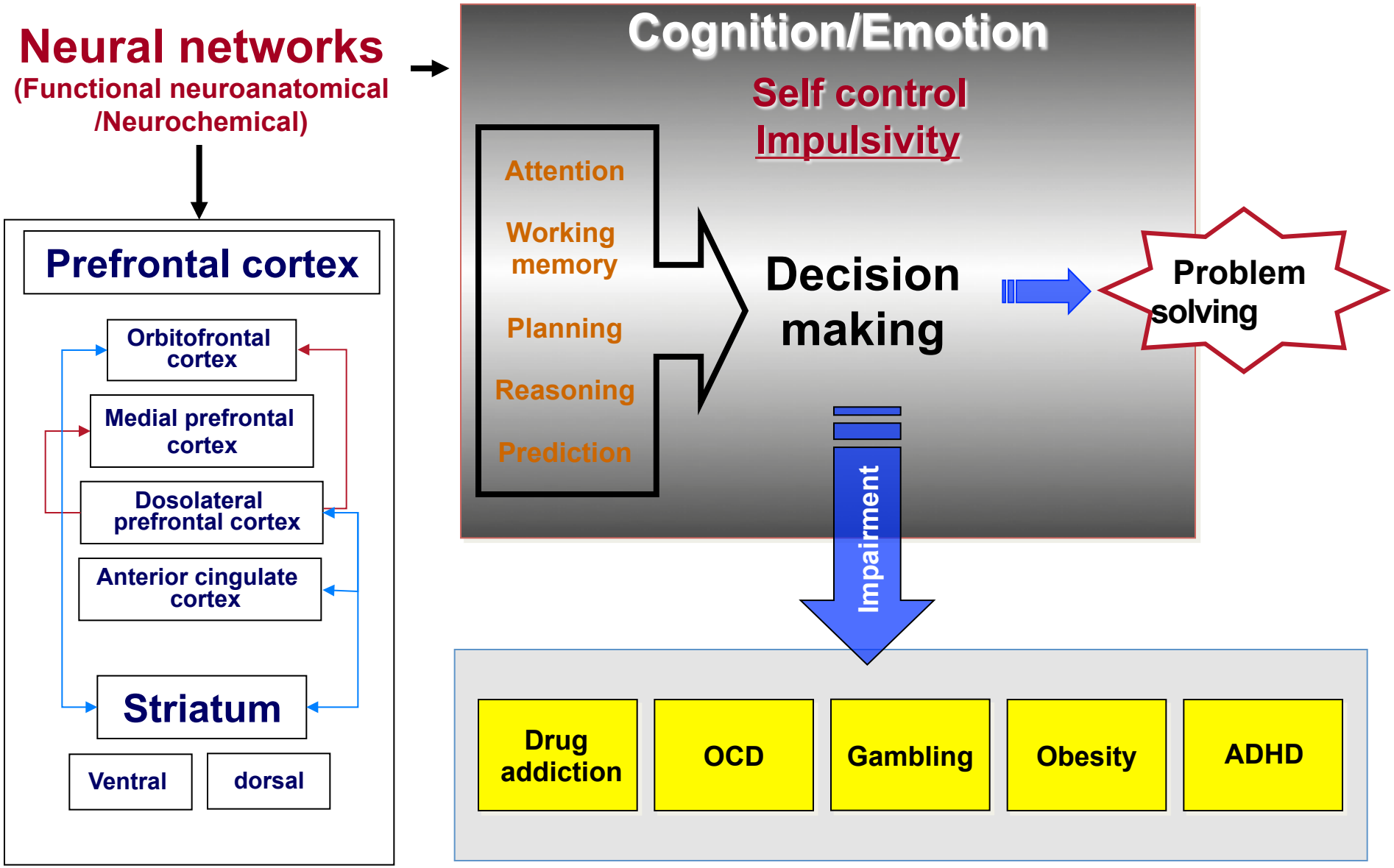
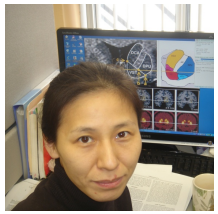
Cho and Strafella 2009

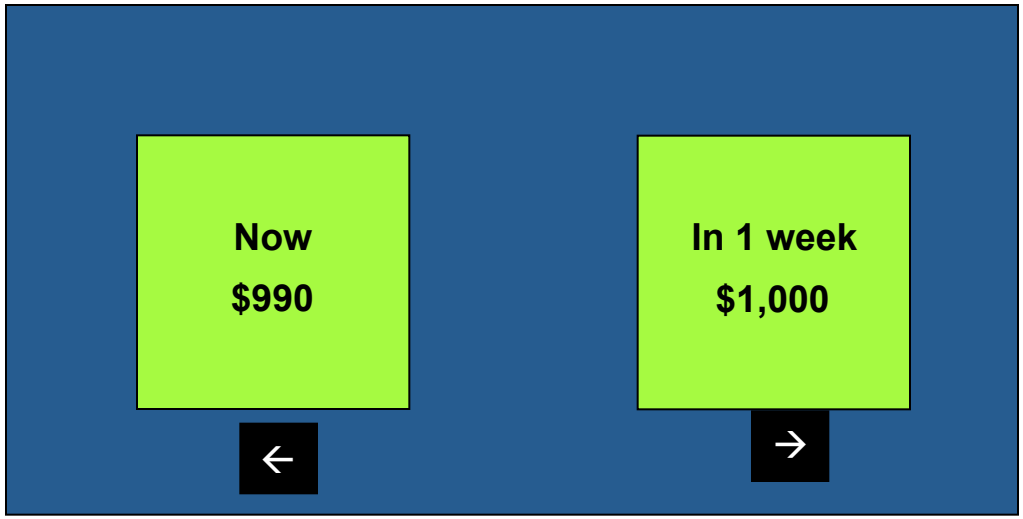

Neural networks
(Functional neuroanatomical /Neurochemical)
Prefrontal cortex
Orbitofrontal cortex
Medial prefrontal cortex
Dosolateral prefrontal cortex
Anterior cingulate cortex
Striatum
Ventral
dorsal
Cognition/Emotion
Self control
Impulsivity
Attention
Working memory
Planning
Reasoning
Prediction
Decision making
Problem solving
Impairment
Drug addiction
OCD
Gambling
Obesity
ADHD

rTMS of Medial Prefrontal Cortex on Delay Discounting Task and Striatal Dopamine



Dr. SS Cho

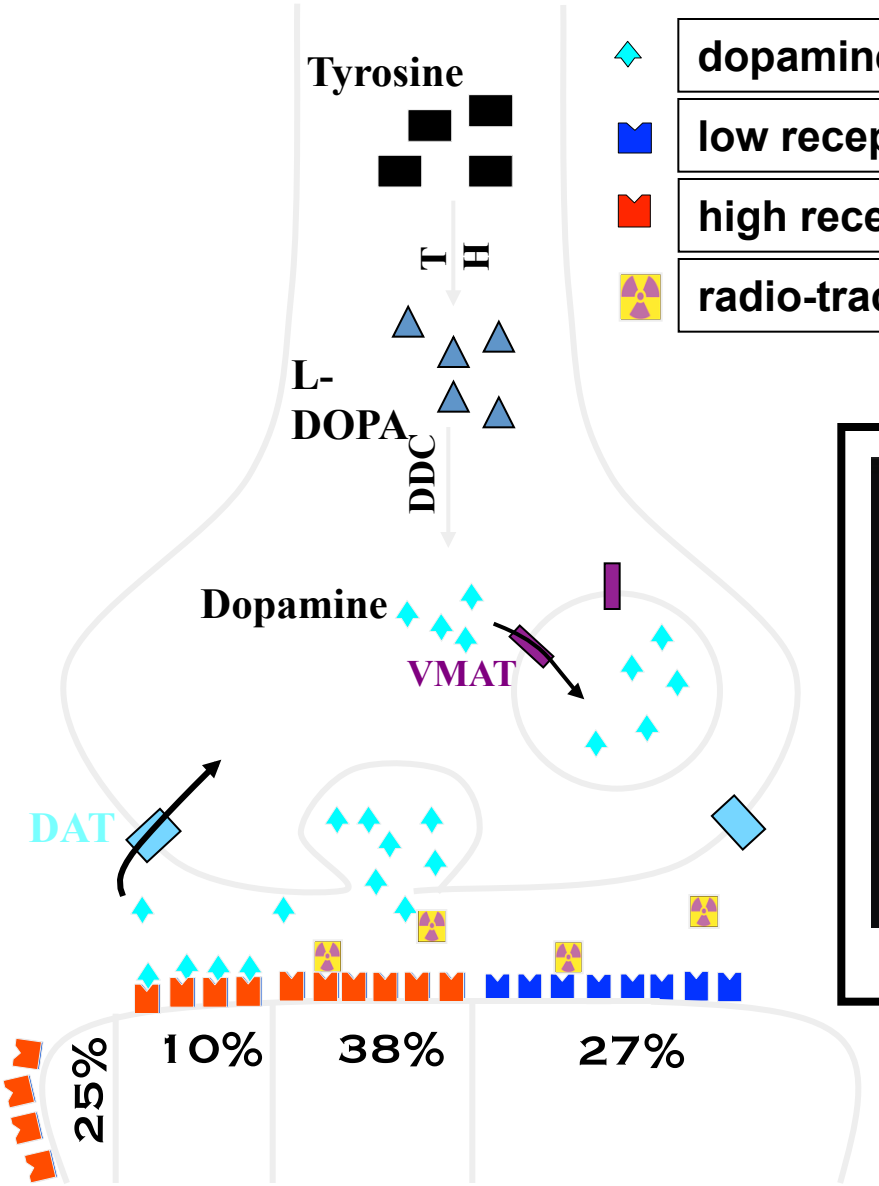
Choice of hypothetical amount of money
Smaller immediate or larger delayed



- Total 150 trials
- randomize for each test

- range of K value: 0.5 ~ 0.0007
- Delay duration: 1 week ~10 years

Post-synaptic Imaging in PD

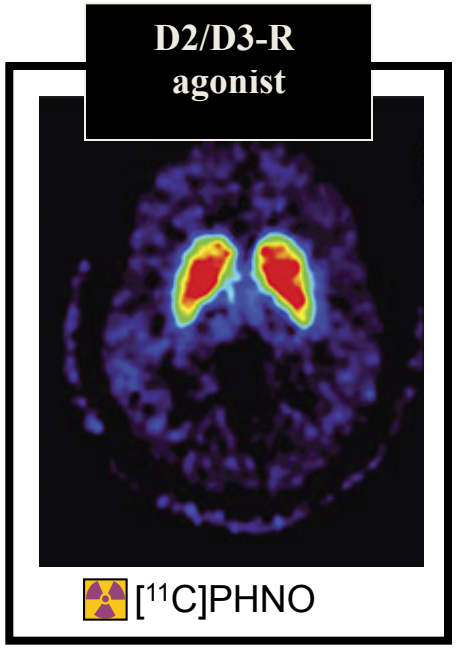


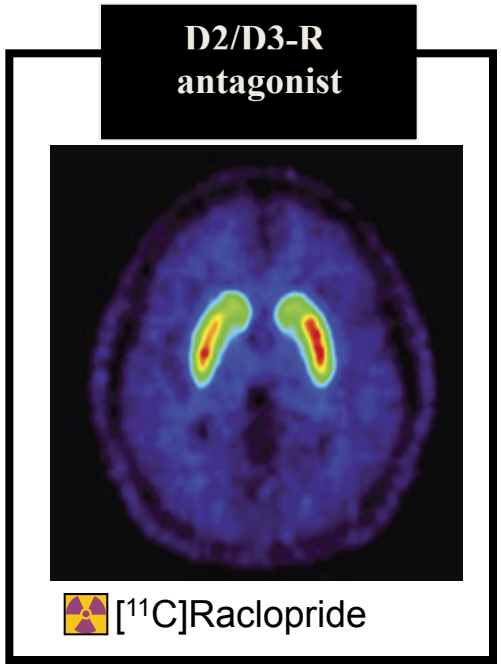
dopamine

low receptor

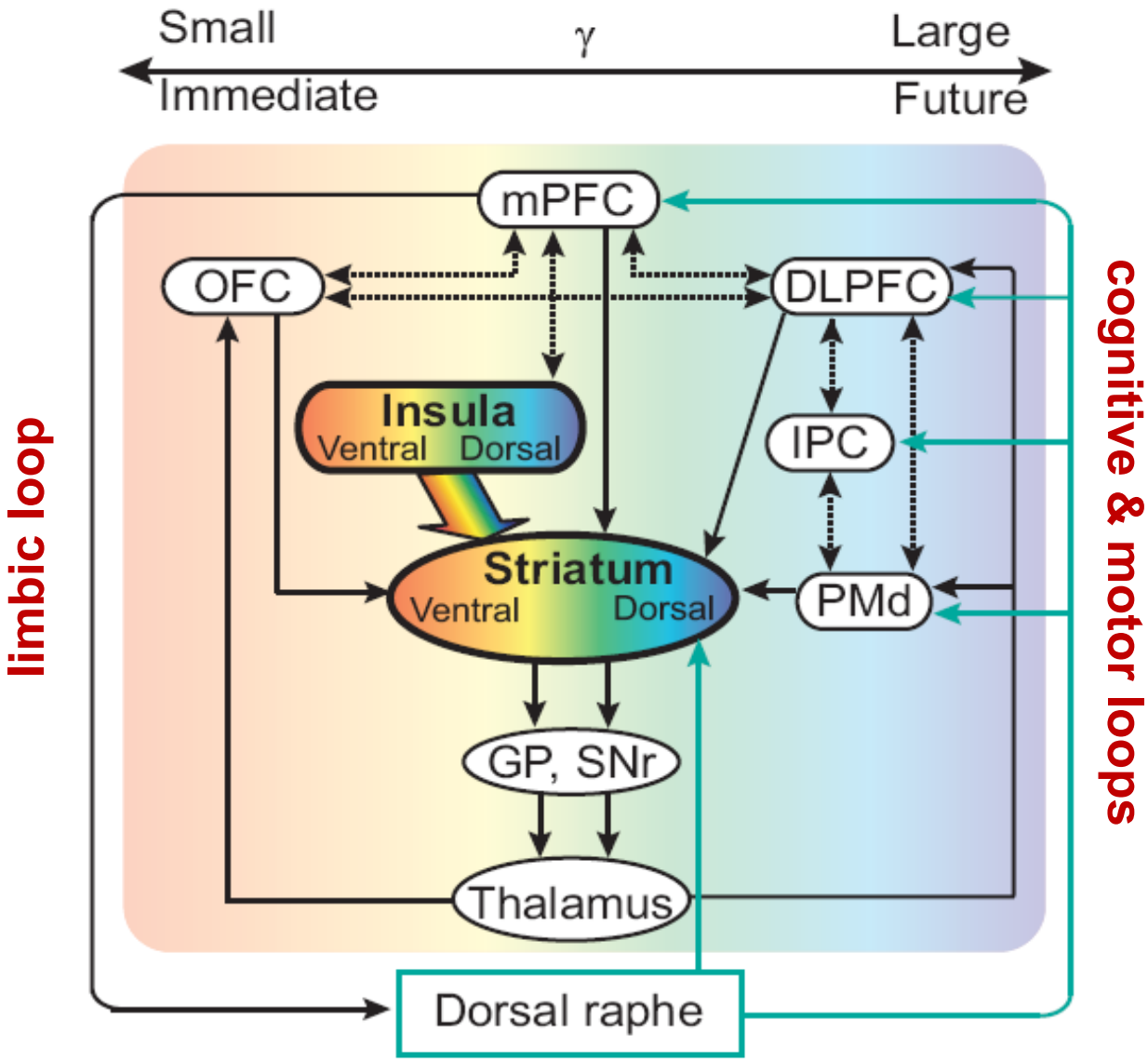
high receptor

radio-tracer



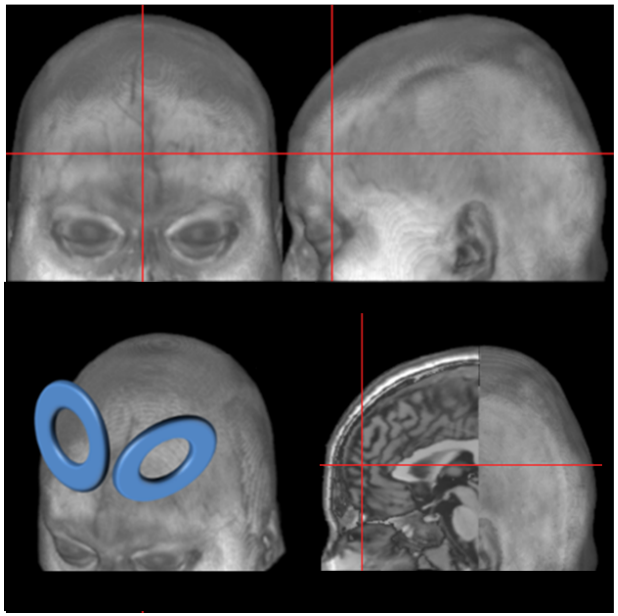


Reward prediction and brain activation

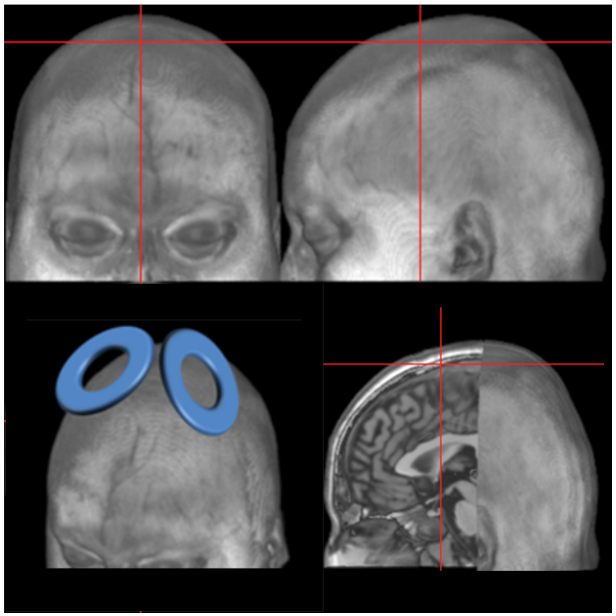


Tanaka et al., 2004

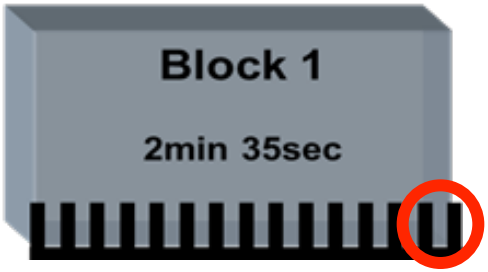
MePFC (x=0, y=59, z=12)



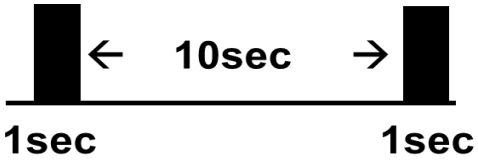
Vertex (x=0, y=0, z=85)



Stimulation Paradigm

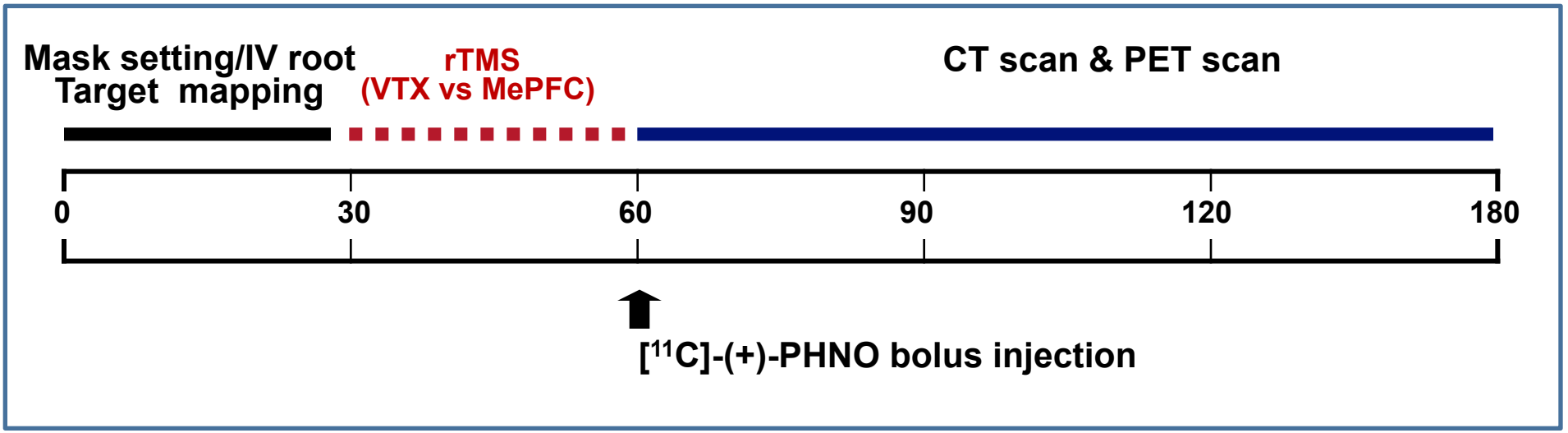


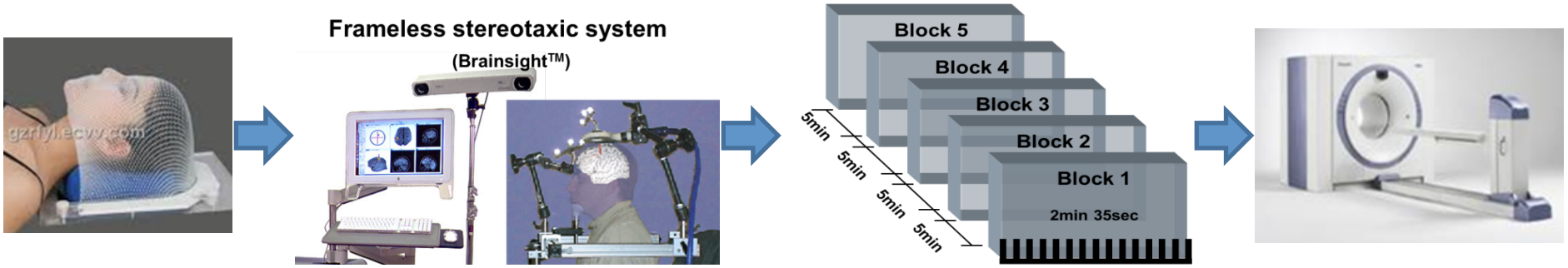
150 pulses/Block



Cho et al., under review

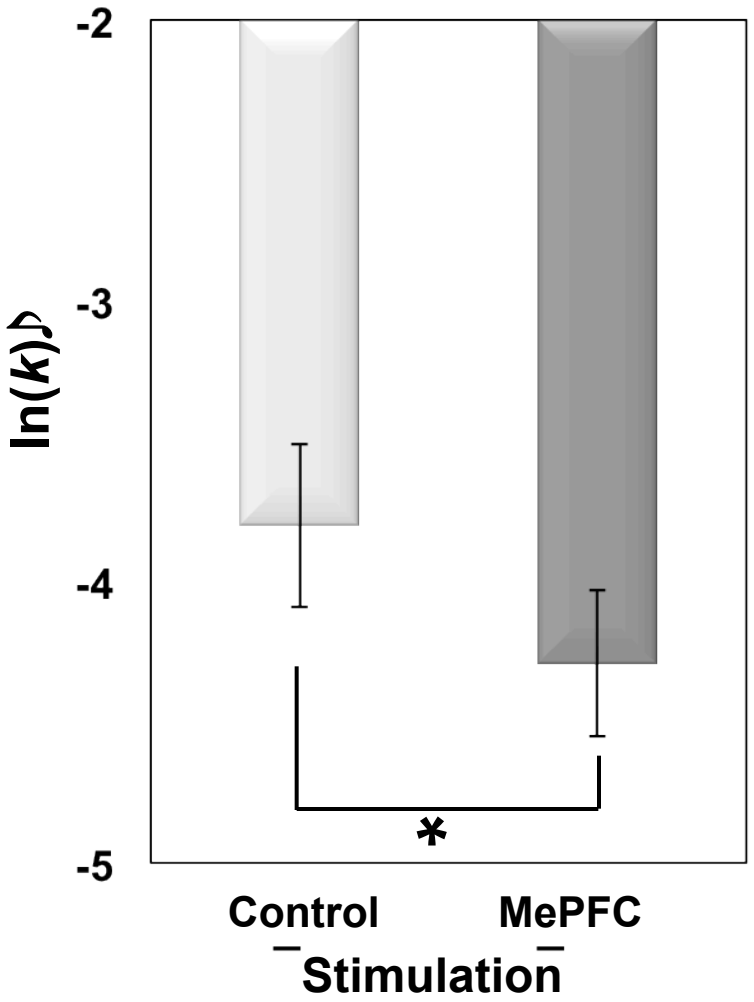
Imaging study protocol



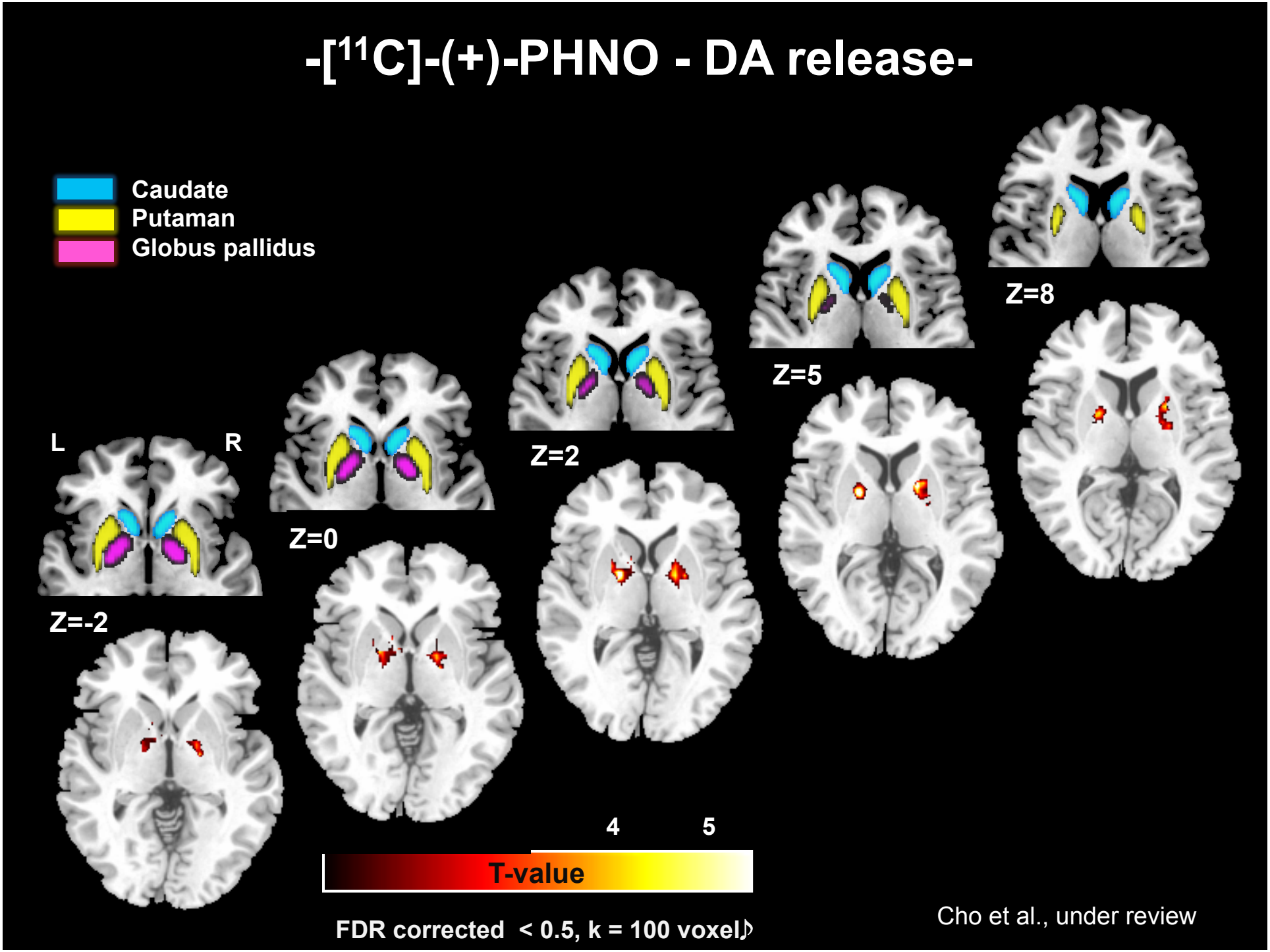


Cho et al., under review

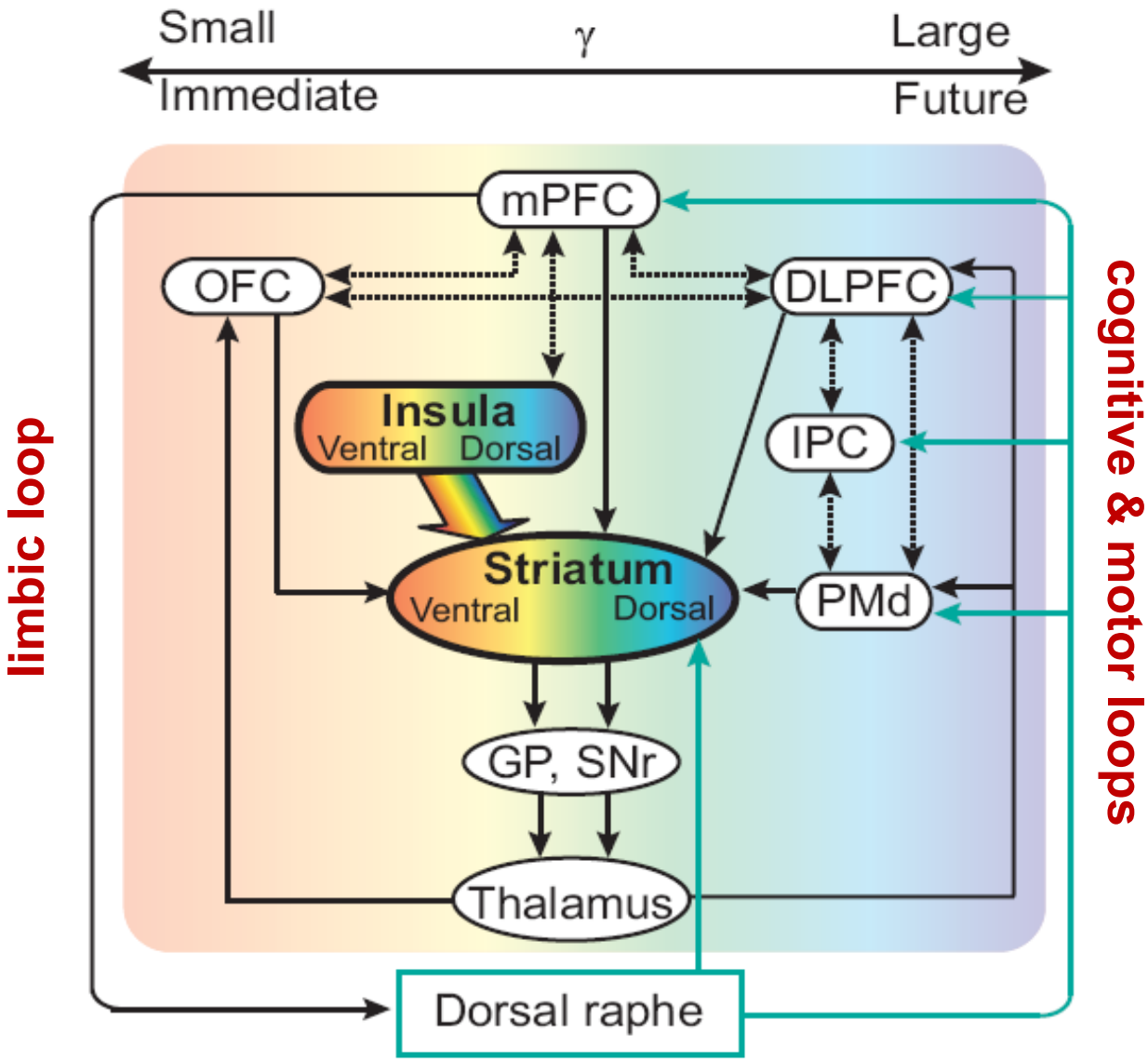
rTMS of Medial Prefrontal Cortex on Delay Discounting Task



Cho et al., under review


-[11C]-(+)-PHNO - DA release-
Caudate
Putaman
Globus pallidus
L
R
Z=-2
Z=0
Z=2
Z=5
Z=8
4
5
T-value
FDR corrected < 0.5, k = 100 voxel♪
Cho et al., under review

Reward prediction and brain activation



Tanaka et al., 2004

Implications

- Functional organization of cortico-striatal fibers and glutamate-dopamine interactions in the human brain: health and diseases.